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SURGERY

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SURGERY

VOL. 40 SEPTEMBER, 1956 NO. 3

Original Communications

A TECHNIQUE FOR TOTAL BODY COOLING OF THE FEBRILE, GRAVELY ILL PATIENT

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ST. PAUL AND MINNEAPOLIS, MINN.

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INTRODUCTION

THIS application of general body cooling grew directly out of our interest in hypothermia as a method of doing open intracardiac surgery.[4, 5] In fact, the first patient we cooled by this technique was a woman who had just undergone repair of an atrial septal defect under direct vision, during hypothermia.

Because of associated mitral valve disease and mild congestive heart failure this 29-year-old woman (U. H. No. 846504) was considered a poor operative risk, but, none the less, the atrial septal defect was repaired and she withstood the immediate consequences of the operation quite well. Approximately six hours after she had been rewarmed, however, her temperature began to climb and it soon reached 104.2° F., rectally. With this her condition deteriorated. Her peripheral pulses were imperceptible, her heart rate was 140, and her blood pressure fell to a level between 50 and 80, systolic. Only with continuously assisted respirations, employing a tracheotomy tube, could cyanosis be prevented. But this was not enough, and her condition seemed to be terminal. At this point, we wrapped her in refrigerating blankets and lowered the temperature rapidly to 96° F. using the same apparatus that had been employed to cool her for the intracardiac operation a few hours earlier. There was a striking improvement in her clinical state.

For several days following this any rise in body temperature above 99° F. would be accompanied by an exhausting respiratory effort and a rapid pulse rate; therefore, her temperature was kept at a slightly subnormal level by intermittent surface cooling for five days. Her final recovery was excellent.

This work was supported by Research Grant H-1374 of the National Heart Institute of the National Institutes of Health, Public Health Service.

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Since this gratifying experience we have used general body cooling to treat 24 other gravely ill, hyperthermic patients. In a few cases there has been a striking improvement while a number of others may have been benefited, at least temporarily.

Mild, general, hypothermia used in this fashion is similar, at least in superficial respects, to the so-called "artificial hibernation" employed by Laborit,[3] and many other European physicians. The European authors have used a number of drugs mixed to make a "lytic cocktail" and then administered this mixture intravenously along with mild surface cooling as part of an anesthetic technique. Good results have been reported but there has been little enthusiasm for the technique in this country as yet. American physicians apparently hold a skeptical attitude toward the theories of the method and the idea of using a mixture of several drugs at once.

There has been some criticism of "artificial hibernation" in Great Britain,[7] and Dundee[2] has, in animal experiments, shed some light on the part drugs play in helping to produce mild degrees of hypothermia. He found that deep anesthesia, curarization, or the "lytic cocktail" were equally effective in facilitating hypothermia and that chlorpromazine alone was apparently as effective as the "lytic cocktail" in potentiating surface cooling. Guided by this work we have used only one or two drugs while reducing the temperature of febrile patients.

The idea of cooling febrile patients is an ancient one.[1] It is only the technique that is new here. With the method to be described the temperature of febrile patients has been reduced to normal or slightly below normal rapidly and conveniently and it has been kept down as long as desired. This method has been briefly described earlier.[6]

METHOD

The patient to be cooled is placed on a large blanket, which consists of two heavy rubberized sheets between which is sewn a long rubber tube (Figs. 1 and 2). This tube runs back and forth the length of the blanket and carries a 50 per cent alcohol or an antifreeze solution which has been cooled by a refrigerating machine.* The machine has both a refrigerating unit and a heating coil so that it may be used either to cool or warm the alcohol reservoir to any desired temperature. In order to lower the body temperature of a febrile patient a blanket temperature of 40° to 50° F. is usually satisfactory. A pump propels this cold solution through the cooling blanket.

Sedation is almost always required but it does not have to be carried to the level of unconsciousness. Enough sedation is used to prevent shivering and though none may be required in comatose patients, large doses may be necessary for obese or delirious individuals. We have relied on chlorpromazine and phenobarbital sodium, both administered intravenously. Fifty milligrams of chlorpromazine are given as soon as shivering appears, and if shivering is still present ten minutes later, 0.13 or 0.20 Gm. of phenobarbital sodium are given. If shivering persists after ten more minutes, a second dose of 50 mg. of chlorpromazine is given. Usually no more than this amount is necessary but in an occasional patient as much as 200 mg. of chlorpromazine has been given within the first two or three hours of cooling. When this heavy dosage is needed we have given no more than two doses of sodium phenobarbital but enough chlorpromazine to definitely stop shivering. It is im-

*Manufactured by the Therm-o-Rite Products Corp., 17 Main St., Buffalo, New York.

portant to suppress even the slight tremor which may be detected by palpating the pectoralis major muscles. In each case the dose of sedative given has depended entirely upon how much was needed to prevent shivering and not on any predetermined schedule.

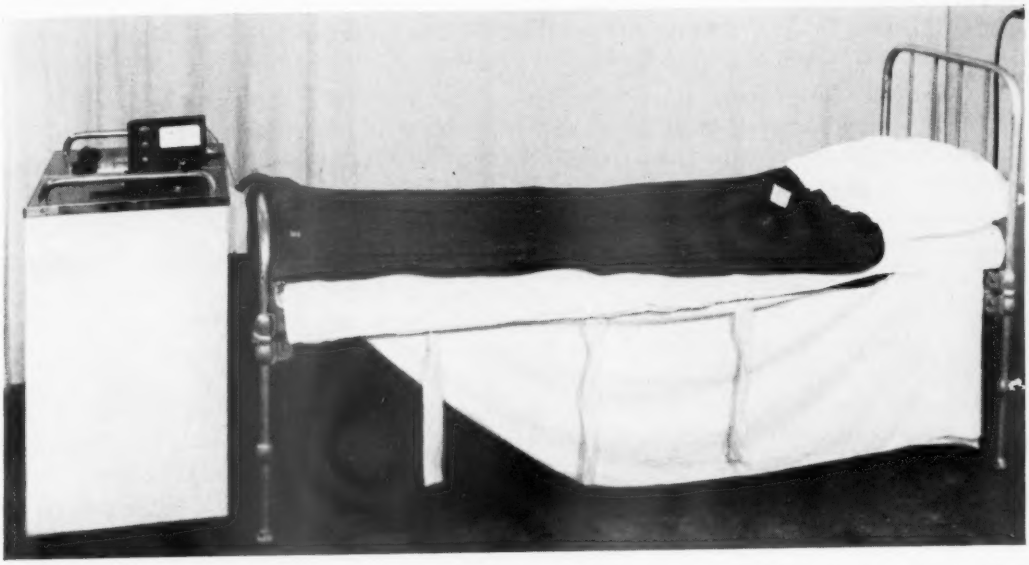

Fig. 1.—Cooling apparatus in position showing the refrigerating machine at the foot of the bed and the uncovered blanket on the bed.

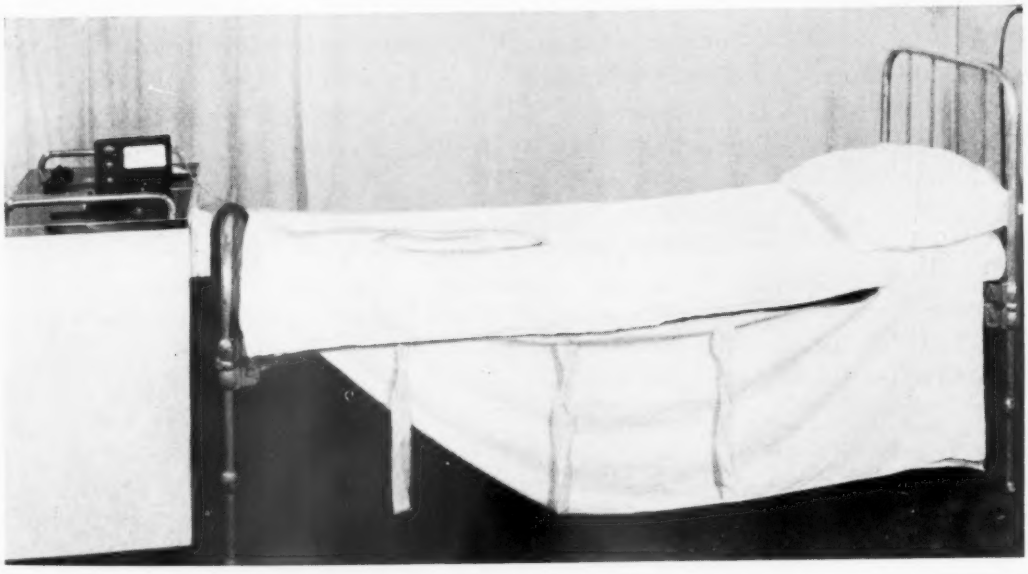

Fig. 2.—A single sheet has been placed over the cooling blanket before laying the patient on it. The electrical thermometer is sitting on the refrigerating machine.

Once the body temperature has started to fall it drops steadily and as it falls below 100° F. the blanket temperature is raised. When the body temperature first drops below 100° F. the blanket temperature is increased from its original level of 40 to 50° F. up to 60 or 70°., then as the body temperature levels off between 95 and 98° F. the blanket temperature may be increased further. To keep the body temperature in this range a blanket temperature no lower than 70 to 80° F. is usually sufficient. Since the

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blanket at this temperature is not cold to touch it is surprising, at first, to see that it is effective in keeping the body temperature down. This is understandable, however, if one places his hand under the back of a patient lying on the refrigerating blanket for the skin is kept at approximately the same temperature as the blanket. A large area of the skin is cooled to room temperature by the circulating fluid in the blanket and this large skin area is effective in cooling the entire body.

When the body temperature falls too low (below 95° F.), the pump is simply turned off and the patient is allowed to rewarm himself. It is inadvisable to warm the patient by heating the blanket for his temperature may then rise too quickly to a febrile level. A careful and continuous observation of the rectal temperature is required so that adjustments of the blanket temperature can be made to avoid unwanted swings in the body temperature. We have used a thermistor type of thermometer to measure temperature, with the sensing element in the rectum.

It is simple to tell when surface cooling is no longer required. Whenever the temperature begins to drop below normal the pump is turned off and therefore, as the patient's tendency to fever abates, the machine is used less and less until it is no longer required during any part of the day. After the initial cooling period it may be necessary to run the pump only in the afternoon and evening. It may not be necessary to use sedation after the temperature has reached normal, but in any case much less is needed than is required during the original cooling period.

CLINICAL MATERIAL

This method of lowering the body temperature has been used only on gravely ill patients whose temperature was 103° F. or higher. The prognosis was poor for all of them and cooling was usually employed during an apparently downward progression in their clinical course. These patients ranged in age from 6 to 84 years with a median age of 59 years. They suffered a wide variety of illnesses and major complications (Table I). Despite the poor outlook before cooling for all of these patients, 13 of the 25 patients treated survived at least one month after the cooling had been stopped.

TABLE I. FEBRILE PATIENTS TREATED WITH SURFACE COOLING

TYPE OF CASE	NUMBER OF PATIENTS	LIVED	DIED
Complications following general surgery (except abdominal cancer)	7	4	3
Complications following surgery for abdominal cancer	5	1	4
Following thoracic surgery	3	2	1
Following urological surgery	2	2	0
Preoperatively (too ill for surgery)	3	0	3
Head injuries or cerebrovascular accident	4	3	1
Burns	1	1	0
Totals	25	13	12

Prior to cooling the body temperature of these patients ranged from 103° to 107° F., rectally. (The highest temperature was in an 84-year-old man who survived.) During the initial cooling period, which took a median time of three hours, the temperature dropped to 99° F. or lower in each patient and there was a concomitant fall in the pulse and respiratory rates.

In 11 patients, 4 of whom survived, the blood pressure was below 100 systolic prior to cooling, despite an adequate blood replacement. In 6 of these 11 patients, the blood pressure rose to 100 systolic or higher after cooling.

Eleven of the patients were comatose before cooling while 9 others were designated as semicomatose or delirious.

DISCUSSION

It is impossible, of course, to be certain that this treatment significantly benefited any of the patients. This was not a controlled experiment and furthermore, the patients were treated by any other means, in addition to cooling, that seemed to have a reasonable chance of helping them. Perhaps other factors were more important than cooling among the patients that recovered. We must proceed cautiously in trying to evaluate the method, but we have the impression, if not the conviction, that some of the patients were helped. The technique has not been clearly harmful for any of them. Body cooling seemed to help all the survivors and for a few it may have been of critical benefit. In addition, cooling appeared to benefit temporarily one half of the patients that died.

As the body temperature decreased the pulse and respiratory rates fell, muscular activity lessened, and the relentless progress to total exhaustion slowed or stopped. This help was not enough if the patient was burdened with too many threatening complications. Occasionally the results of treatment with body cooling were striking but they were not miraculous. Only one survived among the 5 patients who had major complications which caused a high fever after major abdominal operations for cancer (Table I). These patients died with complications such as postoperative hemorrhage, peritonitis, intra-abdominal abscesses, and lung abscess. On the other hand, among patients burdened with merely one major illness, causing a high fever, the results have been better. For example, among the 4 patients in whom the fever was due to brain damage (three head injuries and one cerebrovascular accident), 3 survived.

This technique lowers the temperature of feverish patients effectively and it keeps the temperature down without anesthesia and without much difficulty. The method is easier to use, more certain in its immediate effect, and more continuously effective over a period of hours or days than commonly used cooling procedures such as alcohol sponge baths, ice bags, or aspirin. Two features, particularly, make it a better method of cooling than these other techniques. One is the refrigerating blanket which cools the entire bed and consequently a large skin area. With this large cooling surface, intense cooling is necessary only at first; after the temperature has been lowered the bed surface may be cool enough if it is merely kept at room temperature. The other important feature of the technique is the use of enough sedation to avoid shivering during the initial cooling period. For this purpose, chlorpromazine appears to be especially useful.

The method achieves its objective of eliminating an overwhelming fever without obvious harm and this objective should be a logical one for some

patients. In our experience with a few patients, the treatment has had only a preliminary trial. During this trial it appears to have had value and so we plan to continue using it but now in a controlled, clinical experiment. In this way we hope to make a sound evaluation to support or refute our present impressions.

SUMMARY

1. A convenient, effective method for lowering the body temperature of febrile patients has been described. This method employs a large cooling blanket placed beneath the patient and the use of enough sedation with chlorpromazine and phenobarbital sodium to prevent shivering.

2. Twenty-five gravely ill patients with temperatures above 103° F. have been treated and 13 of them survived.

3. All of the survivors and one half of those that succumbed appeared to be benefited by the cooling technique.

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THE PREVENTION OF VENTRICULAR FIBRILLATION IN EXPERIMENTAL HYPOTHERMIA

Procaine Infiltration of the Superior Atriocaval Junction

Leo R. Radigan, M.D., Thomas A. Lombardo, M.D., and Andrew G. Morrow, M.D., Bethesda, Md.

(From the Clinic of Surgery, National Heart Institute)

THE increased susceptibility of the hypothermic heart to ventricular fibrillation is well recognized. Many recent investigations have been designed to determine the mechanisms involved and means of prevention of ventricular fibrillation in hypothermia. Bigelow[1] reported that the occurrence of fibrillation was associated with a high central venous pressure and could be reversed by phlebotomy. Covino,[2] however, found that venesection did not prevent ventricular fibrillation and concluded that the arrhythmia was not due to cardiac overloading. These same investigators postulated that endogenous epinephrine, released during the cooling, acted upon a sensitized myocardium and produced ectopic foci. Experimental adrenergic blockade, however, failed to afford protection. Edwards[3] demonstrated that the oxygen consumption of the hypothermic heart muscle was reduced but that there was no discrepancy between myocardial oxygen demand and supply. This observation suggests that hypoxia is not a primary factor in initiating ventricular fibrillation during hypothermia.

Montgomery[5] has recently reported that ventricular fibrillation was prevented by perfusion of the coronary arteries with prostigmine. This suggests that a neural component may exist. The present study is a report of experiences with anesthetic blockade of a portion of the extrinsic nerve supply of the heart.

METHODS

Mongrel dogs weighing 8 to 17 kg. were anesthetized with intravenous Pentothal sodium. Small supplemental doses of this agent were given to prevent shivering during the induction of hypothermia. An endotracheal tube was inserted and connected to a demand valve respirator which hyperventilated the animals with 100 per cent oxygen during each experiment. Arterial blood pressures were recorded electrically from an aortic catheter introduced via the femoral artery. The animals were cooled by immersion in an ice bath and body temperatures recorded from a rectal thermometer. When the rectal temperature was 29° C., the animals were removed from the bath and placed upon the operating table. A right thoracotomy was performed and tapes placed about the superior and inferior venae cavae. The azygos vein was ligated and the pericardium opened. At this time the rectal temperature was between 26° and 28° C.

In 20 animals the anatomic area illustrated in Fig. 1 was infiltrated with 5 c.c. of 1 per cent procaine. Eight dogs were given 1 per cent procaine either intravenously or intrapericardially. Twenty additional animals served as untreated controls. Control and test operations were alternated throughout the series.

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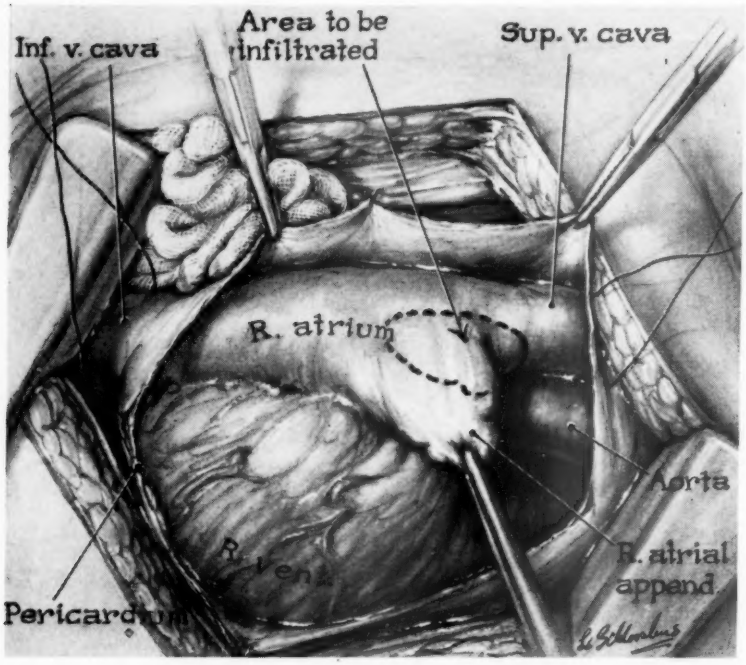

Fig. 1.—The superior atriocaval junction and the area to be infiltrated with procaine.

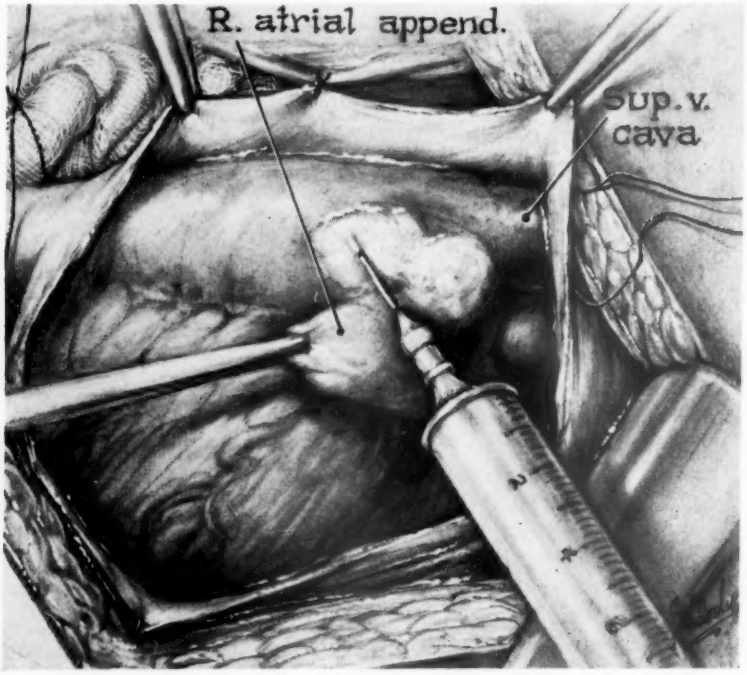

Fig. 2.—Technique of atriocaval infiltration. Confluent subepicardial wheals are raised as in intradermal injection.

A standard operative procedure was then performed in all: venous inflow was occluded for eight minutes. During this period a 4 cm. incision was made into the right ventricle and an exploration of the ventricular cavity carried out. The residual blood was aspirated and the tricuspid valve, pulmonary valve and the papillary muscles were palpated. A figure-of-eight suture was then placed and tied high in the interventricular septum. The cardiotomy was closed with a continuous locking suture of silk near the end of the eight-minute period of inflow occlusion. The superior cava was then released and, sixty to ninety seconds later, the inferior cava. In those animals in which ventricular fibrillation occurred, cardiac massage was carried out for ten to twenty seconds and the heart defibrillated with an electrical shock of 130 volts. After closure of the chest wound, the animals were rewarmed in a water bath at 42° C. until the rectal temperature was 36° C. The respirator was then discontinued and the endotracheal tube removed. Penicillin and streptomycin were given to all animals postoperatively.

The technique of atriocaval infiltration is illustrated in Fig. 2. The injection is made with a 25 gauge needle beneath the epicardium. A series of confluent wheals are raised as in an intradermal injection. We have considered it important to carry the injection well onto both the superior cava and atrial wall anteriorly and posteriorly.

RESULTS

Eighteen of the 20 control dogs developed ventricular fibrillation, an incidence of 90 per cent. All were easily defibrillated; in the majority, a single shock re-established normal rhythm. Occasionally another brief period of massage and a second or third shock were required. Three of these hearts, although defibrillated, never established an effective beat, remained weak and ultimately went into arrest. Ten additional dogs died during the twenty-four hours following the experiment. The mortality was 65 per cent in this control group.

None of the dogs that had the procaine infiltration developed ventricular fibrillation. One died twenty-four hours postoperatively. The surviving animals of both groups exhibited no cardiac or neurologic sequelae. All animals that received procaine intravenously or intrapericardially developed ventricular fibrillation and were sacrificed at the conclusion of the experiment.

DISCUSSION

It should be emphasized that the surgical procedure used in these studies was considered a maximal stimulus to ventricular fibrillation. A simple right ventriculotomy during inflow occlusion may not initiate fibrillation. It appears that mechanical stimulation, particularly of the interventricular septum, is an important factor in consistently producing the abnormal rhythm. In spite of this stimulation, an occasional heart will tolerate the procedure without fibrillating. This was observed in two of the untreated controls of this series.

Undoubtedly the infiltration described affords protection against ventricular fibrillation under the conditions of study. This observation allows speculation as to the etiology of fibrillation during hypothermia. The topical application of procaine to the epicardium is ineffective, as is procaine given intravenously. Apparently, the agent is effective only when placed in the area traversed by the extrinsic cardiac nerve fibers. Similar protection against fibrillation was noted by Riberi, Siderys and Shumacker.[6] In our animals, however, no consistent

changes were noted in the electrocardiographic tracing following infiltration. The present studies would tend to implicate a neural mechanism, involving the extrinsic nerve supply of the heart.

Atriocaval infiltration has been employed in 11 patients undergoing open cardiac operations with hypothermia and inflow occlusion. Other protective measures have not been employed and ventricular fibrillation has not occurred.

In the 18 control animals which developed ventricular fibrillation, the mortality was 65 per cent. These hearts were defibrillated easily yet the majority of the animals died. Physiologic and pathologic findings suggest that the cause of death was myocardial failure. These studies will subsequently be reported in detail.[4]

SUMMARY

Procaine infiltration of the superior atriocaval junction prevented ventricular fibrillation in 20 hypothermic dogs subjected to right ventriculotomy. Among 20 control dogs, the incidence of ventricular fibrillation was 90 per cent.

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HYPOTHERMIC VENTRICULAR FIBRILLATION AND ITS CONTROL

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INTRODUCTION

THE performance of intracardiac surgical procedures under direct vision is limited at present by the duration of circulatory stasis considered safe. At normal temperature the maximum period is two to three minutes. The depression of metabolic rate incident to hypothermia may extend this period safely to ten to twenty minutes, depending upon the degree of hypothermia induced. This latter period is probably adequate for most of the presently contemplated types of surgical repair. Theoretically, therefore, the variety of patients who might benefit by surgery is greatly increased by the use of hypothermia.

To date, however, the advantages afforded by hypothermia have been counterbalanced to a considerable extent by the coincident hazard of increased myocardial excitability leading to ventricular fibrillation.[4, 5] It has been demonstrated that the heightened myocardial irritability associated with hypothermia is the consequence of a concomitant respiratory acidosis. When the systemic pH is maintained near normal by controlled artificial respiration in experimentally induced hypothermia the excitability of the ventricle also remains normal.[6] Although spontaneous ventricular fibrillation at low temperature can be prevented in this manner,[6, 9, 12] a normal pH alone may not provide adequate antifibrillary protection when the hypothermic ventricle is further subjected to insult by direct surgery.[11] Thus, some means of augmenting the beneficial effects of controlled ventilation is required for complete protection against fibrillation before hypothermia can be widely advocated as an adjunct to cardiac surgery.

The basic cause of cardiac arrhythmias is still unknown. But pharmacologic agents capable of preventing or arresting abnormal rhythms have long been sought. Those drugs in clinical use which have previously been tested under conditions of hypothermia have been found wanting.[7] Recently Clark and associates[10] have demonstrated that the new procaine derivative Ambonestyl† (2-diethylaminoethyl-isonicotinamide) was effective in the control of arrhythmias due to coronary ligation in the dog. In addition Clark and Etsten[3] reported that Ambonestyl possessed antiarrhythmic effects in

This investigation was supported by Contract AF 18(600)-65 with Wright Air Development Center, Wright-Patterson Air Force Base, Ohio.

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*The research was performed during the senior author's tenure of a Life Insurance Medical Research Fellowship.

†E. R. Squibb & Sons through the courtesy of Dr. Byron Clark, Tufts University Medical School.

patients with a variety of auricular and ventricular abnormalities. In consequence of these reports the efficacy of Ambonestyl as an antifibrillary agent in experimental cardiac surgery at low body temperatures was investigated, and the results form the basis of this study.

METHODS

Forty-five healthy mongrel dogs of both sexes and indeterminate ages, ranging from 9.8 to 19.4 kg., were anesthetized with intraperitoneal pentobarbital sodium (30 mg./kg. body weight) and subjected to the following preimmersion procedures: endotracheal intubation, insertion of a rectal thermocouple, placement of electrocardiographic limb leads, exposition of the right external jugular vein for injections and withdrawal of blood samples. The right common carotid artery of 10 of the Ambonestyl-treated dogs was exposed for the manometric recording of mean arterial pressure. Rectal temperature was recorded via Speedomax* in degrees C.

When a hypothermic temperature of 25° C. was achieved by immersion in an iced bath, 40 of the dogs were removed from the bath for the following surgical procedures: Right thoracotomy at the fifth intercostal space was performed and the ribs retracted. The superior and inferior venae cavae and the azygos vein were clamped, and the pericardium incised longitudinally. An incision of approximately 2.5 cm. was made through the right ventricular wall and the interior of both the right ventricle and auricle was palpated with a finger. In those dogs which escaped ventricular fibrillation the incision was closed with 4 or 5 sutures and the circulation was reestablished. The total time of venous occlusion was in every instance 15 minutes. The average rectal temperature at the time of ventriculotomy was 23.9 ° C. The chest was then closed, the pneumothorax reduced, and rewarming instituted by immersion in a 42 to 48° C. bath.

Since sterile procedures were not employed most of the dogs were sacrificed on return to normal body temperature. Five dogs were given 600,000 units of Penicillin intramuscularly and observed for two to six weeks postoperatively.

Artificial respiration with room air was administered to all dogs during the period of pneumothorax and to 20 dogs (Groups 2 and 4) throughout the period of cooling. The latter procedure ensured maintenance of a blood pH above 7.3. For the pH measurements on jugular blood a Cambridge pH meter was employed. The electrode was equipped with a water jacket for temperature control and the jacket temperature was in every instance set at the prevailing rectal temperature.

Ambonestyl was administered to 2 groups of dogs via the jugular vein when rectal temperatures reached 30° C. Forty mg. per kg. were dissolved in 20 ml. of isotonic saline solution and injected over a five-minute period. The operative procedures described above were performed within twenty to forty-five minutes after the injections, that is, when the rectal temperatures reached 24° C.

Ventricular excitability was measured in 5 Ambonestyl treated dogs. These animals were not subjected to surgery, but were cooled to terminus. Ambonestyl (40 mg. per kg.) was administered at normal temperature and at hourly intervals during cooling in this series. Ventricular thresholds were determined immediately before and after the injection of the drug at normal temperature and at 30° C. and 23° C. The method used to determine ventricular threshold has been described elsewhere.[4]

RESULTS

Control Studies.—The 10 dogs of Group 1 respired spontaneously while cooling and thus suffered a fall in blood pH to a mean of 7.15 at 25°. Eight of these animals died of ventricular fibrillation (V.F.) in consequence of the incision or the subsequent suturing of the ventricle. The 2 dogs surviving the

*Leeds-Northrup.

procedure were rewarmed. One of these exhibited signs of cardiac hypoxia. Partial atrioventricular block appeared shortly after chest closure and ventricular standstill occurred after rewarming to 30° C. The second dog was sacrificed after rewarming to 37° C.

Artificial Hyperventilation.—The venous pH was maintained between 7.3 and 7.6 in the second group of 10 dogs via controlled respiration. It had been demonstrated that in this pH range spontaneous V.F. did not occur.[6] The additional surgical insult, however, caused V.F. in 4 of these dogs. Six were successfully rewarmed to 37° C. Five dogs were sacrificed and one was observed during the following six weeks and then sacrificed. Post-mortem examination revealed a completely healed ventricle without evidence of pathology other than the scar at the site of the incision.

The beneficial influence of hyperventilation for pH control during hypothermia is striking when one considers that in its absence the incidence of V.F. in nembutalized acidotic dogs is greater than 60 per cent[4, 6] even without the additional trauma of ventriculotomy.

Ambonestyl.—Ten dogs respired spontaneously during cooling, and in consequence had a mean venous pH of 7.13 at 25° C. Intravenous Ambonestyl (40 mg. per kg.) was administered at 30° C. The injection was followed by a transient drop in arterial pressure averaging 20 mm. Hg. Neither the ECG nor pulse rate appeared in any way affected, nor were other side effects observed. Three of these dogs suffered V.F. during the surgical procedures and seven were rewarmed to normal temperature and sacrificed. None of the latter exhibited cardiac arrhythmias during surgery or rewarming. These numbers again stand in sharp contrast to the 80 per cent incidence of fibrillation in the untreated control series. Ambonestyl alone thus exerts a considerable degree of protection against V.F. under conditions of hypothermic cardiac surgery.

Ambonestyl and Artificial Ventilation.—In view of the beneficial effects which pH control and Ambonestyl exerted individually it appeared that acting in combination these effects might be summed. A fourth group of 10 dogs was therefore subjected to hypothermia under artificial respiration, with administration of Ambonestyl after cooling to 30° C. A synergistic action is revealed in the fact that all 10 dogs survived the surgery and, with one exception, the rewarming to normal temperature. The exception was again one which showed signs of cardiac hypoxia similar to that described for a member of the control series. The electrocardiogram during rewarming showed a progressive atrioventricular block, with ventricular arrest at 32° C.

Of the other 9 dogs 5 were sacrificed immediately on return to normal temperature, and 4 were maintained for two to four weeks for observation. All appeared in excellent health at the time of sacrifice. In only one of the 4 dogs was there any evidence of an infarct. This was of small size on the endocardial surface at the site of the incision, and was well healed.

Table I summarizes the data for each of the 4 groups. Clearly indicated is the antifibrillary protection afforded by normal or slightly supernormal pH and by Ambonestyl individually, and their summed effects when acting concurrently.

TABLE I

SERIES	CONTROL (pH 7.05-7.20)	HYPERVENTILATION (pH 7.30-7.60)	AMBONESTYL (pH 7.08-7.16)	AMBONESTYL (pH 7.30-7.60)
Number of dogs	10	10	10	10
Number of fibrillators	8 (80 per cent)	4 (40 per cent)	3 (30 per cent)	0
Number of nonfibrillators	2 (20 per cent)	6 (60 per cent)	7 (70 per cent)	10 (100 per cent)

Fig. 1 shows electrocardiographic records of a representative dog in this series taken *A*, before cooling, *B*, immediately after ventriculotomy at 23° C., *C*, after rewarming to 37° C., and *D*, three weeks postoperatively. The electrocardiographic records of all the chronic and acute dogs successfully rewarmed were equally free of abnormalities.

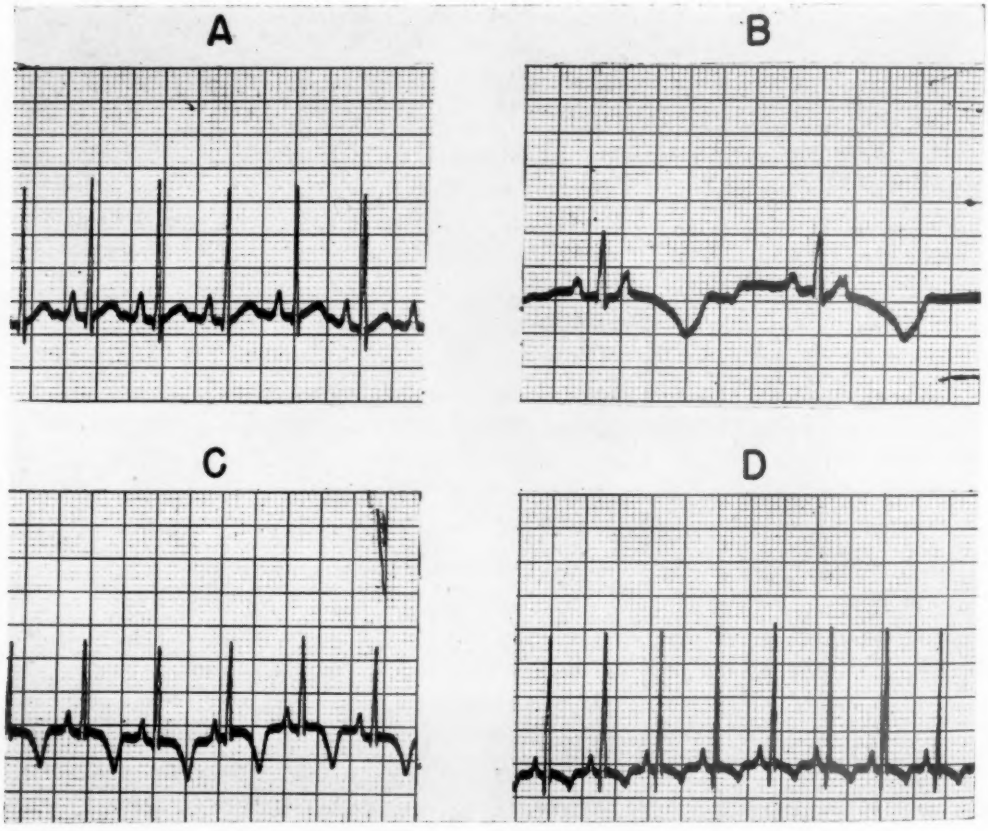

Fig. 1.—Electrocardiograph recordings from a representative dog of group 4. Pentobarbital anesthesia, normal pH during hypothermia induction and treatment with Ambonestyl. *A*, before cooling; *B*, immediately following right ventriculotomy at 23° C.; *C*, after rewarming to 37° C.; and *D*, 3 weeks postoperatively.

Mode of Action of Ambonestyl.—In an effort to elucidate the nature of the antiarrhythmic action of Ambonestyl at low temperatures, ventricular excitability[8] was studied in 5 additional dogs cooled to terminus. At 38° C. the threshold of the ventricle remained unchanged following the injection of the agent. This is consistent with the findings of Clark and associates.[10] During

cooling, at 30° C. and 23° C. the threshold also showed no basic change despite the progressive development of an acidotic state. Death was in every instance due to asystole which occurred after cooling to 17° C. or lower. Thus Ambonestyl apparently exerted its antifibrillary action at low temperature by preventing the fall in ventricular threshold usually observed in untreated acidotic, hypothermic dogs.

DISCUSSION

The use of hypothermia as an adjunct to cardiac surgery has heretofore been limited due to the high incidence of ventricular fibrillation encountered while manipulating the hypothermic heart.[1, 2] The report of Swan and associates[13] and the data presented herein indicate that maintenance of a normal pH by hyperventilation during cooling is of itself a very considerable protection, but for ventriculotomy it remains in some measure inadequate to eliminate the danger of ventricular fibrillation when surgery is instituted. Thus some additional means of preventing the occurrence of ventricular fibrillation must be sought.

Montgomery and associates[11] have reported that hyperventilation and intracoronary injections of Prostigmine are capable of preventing the onset of the fibrillary process in hypothermic dogs subjected to cardiac surgery. However, heart rates of 10 to 25 beats per minute were required to insure success so that cardiac arrest becomes a danger. The data presented herein attest to the efficacy of another pharmacologic agent, Ambonestyl, as an antifibrillary drug under conditions of hypothermic cardiac surgery. Ambonestyl per se prevented the occurrence of ventricular fibrillation in 70 per cent of the experimental subjects. In combination with controlled respiration this agent provided 100 per cent protection in our hands. There appears to be little danger of cardiac arrest with Ambonestyl since at no time did the heart rate fall below 40 beats per minute in any dog at 24° C.

Ambonestyl thus appears to possess great virtue as an antifibrillary drug under conditions of hypothermia. In addition to its protective action in this experimental study, Clark and associates[3, 10] have also demonstrated its antiarrhythmic action in the "coronary" dog and in a varied group of cardiac patients. Its toxic effects appear to be relatively insignificant. Aside from the slight transient fall in blood pressure observed in the present study, it exerts no undesirable effects on the cardiovascular system and only a slight excitatory effect on the central nervous system.[10] In addition it has the advantage of being rapidly absorbed from the gastrointestinal tract and so is effective orally. Although Ambonestyl does not alter the excitability of the normothermic ventricle, it appears to prevent a fall in threshold during cooling. This action apparently is responsible for its antiarrhythmic effect in hypothermia with or without the added stress of cardiac surgery.

The occurrence of ventricular arrest in two dogs during rewarming indicates that circulatory stasis of fifteen minutes' duration at a rectal temperature of 25 to 23° C. may not be entirely safe. The electrocardiographic patterns in these two dogs were definitely suggestive of myocardial hypoxia. Moreover, Williams and associates[14] have reported that circulatory occlusion of

10 to 12 minutes at rectal temperatures of 28 to 25° C. produces definite central nervous system abnormalities. Thus, it would appear that a temperature of 20° C. would be more favorable for the performance of intracardiac procedures which require stasis for 15 minutes. At 20° C. one would obtain the full benefits of hypothermia since at this temperature oxygen consumption is only 25 per cent of normal. There is little reason to doubt that controlled pH with Ambonestyl will afford equivalent protection at 20° C. provided an additional injection of the drug is given within thirty minutes of surgery.

SUMMARY AND CONCLUSIONS

Eighty per cent of nembutalized dogs succumb to ventricular fibrillation during ventricular surgery at 25 to 23° C. when an acidotic state is allowed to occur during cooling. Maintenance of normal or slightly supernormal pH by hyperventilation reduces the incidence of ventricular fibrillation to 40 per cent. Only 30 per cent of hypothermic acidotic dogs suffer this cardiac abnormality when pretreated with Ambonestyl. A combination of controlled ventilation and Ambonestyl provides absolute (100 per cent) antifibrillary protection during hypothermic cardiac surgery. The occurrence in two cases of ventricular standstill due apparently to myocardial hypoxia indicates that fifteen minutes of circulatory stasis is not entirely safe at 25° C. The suggestion is made that conditions for intracardiac surgery may be more favorable at a somewhat lower temperature.

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STRUCTURAL CHANGES IN THE HEART RESULTING FROM CARDIAC MASSAGE

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MANUAL compression of the heart is the most effective resuscitative measure in the management of cardiac arrest, and the technical details of performing this emergency procedure are well established. Little attention has been directed, however, toward the structural changes in the heart that may result from cardiac massage. This report is concerned with such alterations as observed in the hearts of 14 patients on whom cardiac massage was performed and who died subsequently.

OBSERVATIONS

Among the 14 patients studied, 7 died immediately of cardiac arrest, one died at the end of six hours, and the remaining 6 between ten and seventy-nine days later. Of these 6 patients, 3 died of cardiac arrest, while 3 regained consciousness and later died of their primary disease.

TABLE I. CHANGES IN THE HEART CAUSED BY CARDIAC MASSAGE

PATIENT	AGE RACE SEX	DURATION OF MASSAGE (MINUTES)	DAMAGE TO		SURVIVAL (DAYS)	PERICARDIUM	VENTRICULAR FIBRILLATION
			EPICARDIUM	MYOCARDIUM			
Immediate group							
I-1 N-72-53	30; N; M	1	None	None	6 hrs.	Not opened	0
I-2 N-39-53	58; N; M	3	None	None	0	Not opened	0
I-3 N-55-53	62; N; M	15	None	None	0	Not opened	0
I-4 N-223-53	38; N; M	15	None	None	0	Not opened	0
I-5 N-257-54	38; N; M	60	Severe	Severe	0	Not opened	Present
I-6 N-14-55	34; W; M	120	Severe	Rupture	0	Opened	Present
I-7 N-153-55	26; W; M	150	Severe	Severe	0	Opened	Present
I-8 N-97-51	33; N; M	300	Severe	Severe	0	Opened	Present
Early group							
E-1 N-114-53	64; W; M	1	Severe	None	12	Not opened	0
E-2 N-7-51	23; W; M	4	Moderate	None	10	Not opened	0
E-3 N-14-54	51; W; M	6	None	None	24	Opened	Present
E-4 N-138-50	38; N; M	12	Moderate	Moderate	10	Not opened	0
Late group							
L-1 N-38-53	43; W; M	1	Moderate	None	79	Not opened	0
L-2 N-71-53	50; W; M	1	Severe	None	63	Opened	0

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The hearts removed at necropsy were fixed in formalin, 10 per cent, and subsequently examined grossly and microscopically. The structural changes in the massaged hearts were classified as having occurred: (1) immediately, (2) from one week to one month after massage, and (3) after two months (Table I).

Fig. 1.

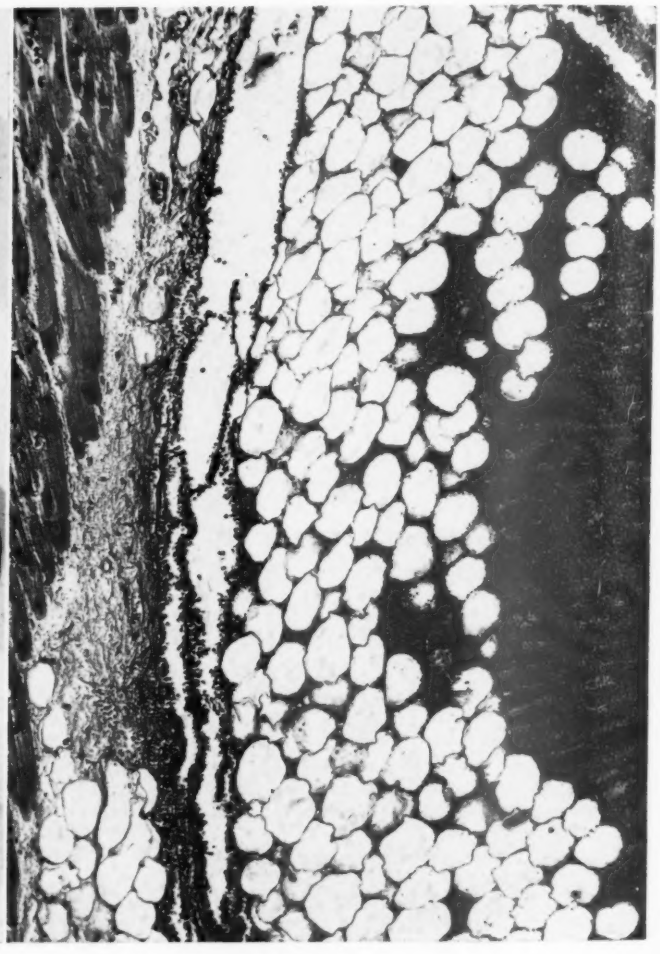

Fig. 2.

Figs. 1 and 2.—The heart of a Negro man, aged 38 years (I-5; Table I), massaged for one hour after cardiac arrest without response. There are extensive epicardial and myocardial hemorrhages. Microscopically, extravasations of erythrocytes are between the adult adipose tissue cells of the epicardium.

Immediate Change.—In the 7 patients who died immediately following the massage and in the one who died at the end of six hours, there was a hemorrhagic pericardial effusion. In four of these the surface of the heart revealed, as evidence of the massage, ecchymoses and petechial hemorrhages in the epicardium and gross hemorrhages in the myocardium (Figs. 1 to 4). Microscopically there were extravasations of erythrocytes in the myocardium so extensive that in places the muscle fibers were spread apart. The epicardium was focally and diffusely infiltrated with aggregations of erythrocytes. The clinical data and findings at necropsy in one patient who died of rupture of the heart are given below.

H. M., a 34-year-old man (I-6) was admitted to the Veterans Administration Hospital, Houston, Tex., with a diagnosis of bleeding duodenal ulcer. His condition failed to improve on conservative management and therefore a gastric resection and gastrojejunostomy were performed. On return to the ward cardiac arrest occurred. The chest was opened immediately and the heart massaged. After 90 minutes the myocardium ruptured over the left ventricle just below the atrioventricular groove. The rupture was closed and massage continued for 30 more minutes without response. At necropsy (N-14-55) the surfaces of both ventricles were discolored and hemorrhagic. The area of rupture was sutured with interrupted black silk. On parallel cut surfaces perpendicular to the axis of the heart the lumen of the left coronary artery was narrowed to pin point by atherosclerotic change (Fig. 3).

Fig. 3.

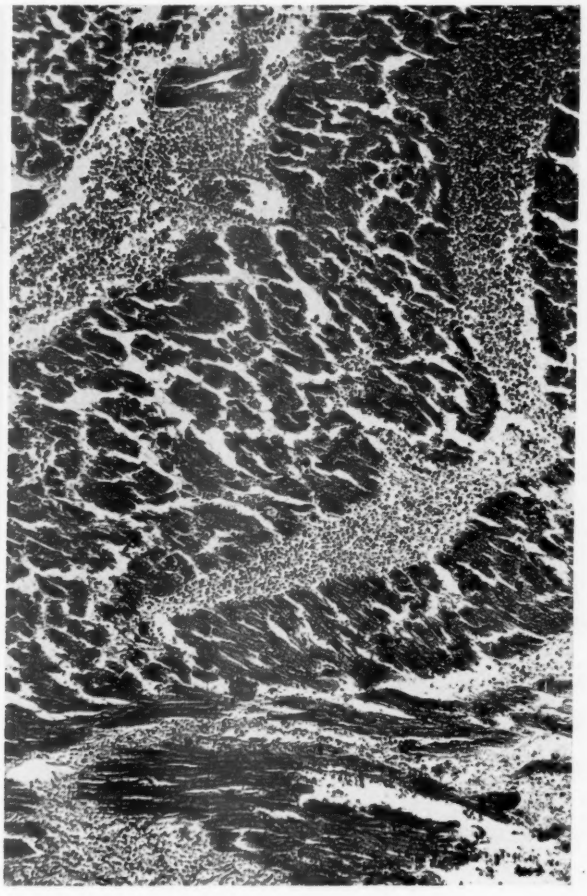

Fig. 4.

Figs. 3 and 4.—The heart of a man, aged 34 years (I-6; Table I), massaged for ninety minutes, at which time it ruptured over the left ventricle just below the atrioventricular groove. The rupture was closed and massage continued for thirty more minutes. On parallel cut surfaces perpendicular to the axis of the heart the lumen of the left coronary artery is narrowed to pin point by atherosclerotic change. There are extensive areas of hemorrhage scattered throughout the substance of the myocardium and epicardium. Microscopically, broad zones of extravasated erythrocytes separate myocardial fibers.

Microscopically there were focal extravasations of erythrocytes in the adipose tissue of the epicardium and in the myocardium with separation of the myocardial fibers (Fig. 4). There was intimal thickening in the coronary arteries with diminution of the lumen in some areas and obliteration in others.

The acute coronary occlusion with the resulting ischemia is presumed to have contributed to the rupture of the myocardium. This association has been noted previously.[1, 3, 4]

Early Changes.—In each of the 4 patients who survived cardiac massage for from one week to one month there was a hemorrhagic pericardial effusion. In three of these the effusion had become turbid. Microscopically there was a minimal pericardial reaction consisting of infiltration of lymphocytes, plasma cells, and large mononuclear cells. Residual myocardial damage, consisting of an infiltration of the muscle bundles by focal aggregation of neutrophilic granulocytes, was observed in one patient. The clinical data and findings at necropsy of one of the patients in this group are given below.

Fig. 5.—Focal infiltrations of granulocytes between fibers of the myocardium, in a Negro man aged 38 years (E-4; Table I), who died of septicemia ten days after cardiac arrest and massage.

J. C., a 38-year-old Negro man (E-4), was admitted to the Veterans Administration Hospital, Houston, Tex., with acute abdominal pain. A diagnosis of acute pancreatitis was made and he was treated with antibiotics, atropine, nasogastric suction, narcotics and splanchnic block. Because of persistent fever, abdominal pain, and a mass in the right upper portion of the abdomen, a laparotomy was performed twenty-five days following admission. An abscess in the lesser omentum was drained and the gallbladder removed. During the procedure cardiac arrest occurred and the heart was first massaged through the diaphragm, then the chest was opened and direct cardiac massage was given without opening the pericardium. After twelve minutes of massage cardiac action resumed. The patient regained consciousness on the second day and continued to improve. On the tenth day after operation blood was noted in the gastric drainage and there was oozing from the wound. Then the patient became deeply icteric and after two severe bleeding episodes died. Necropsy (N-138-50) revealed massive hemorrhage into the lesser omental sac and severe hemorrhagic pancreatitis with widespread fat necrosis. The pericardial cavity contained 20 cc. of red turbid fluid. Microscopically the myocardium was infiltrated with focal aggregations of neutrophilic granulocytes (Fig. 5).

Late Changes.—In the two patients who died sixty-three and seventy-nine days, respectively, following massage, there were changes in the pericardium. In one of the patients (L-2) the pericardial cavity was obliterated by delicate and dense fibrous adhesions and the epicardium was thickened. In the other patient (L-1) the pericardial reaction was less severe, and microscopically a thin layer of connective tissue interspersed with chronic inflammatory cells covered the surface. In neither instance was there any evidence of residual damage to the myocardium. The clinical data and findings at necropsy of one of these patients are given below.

Fig. 6.

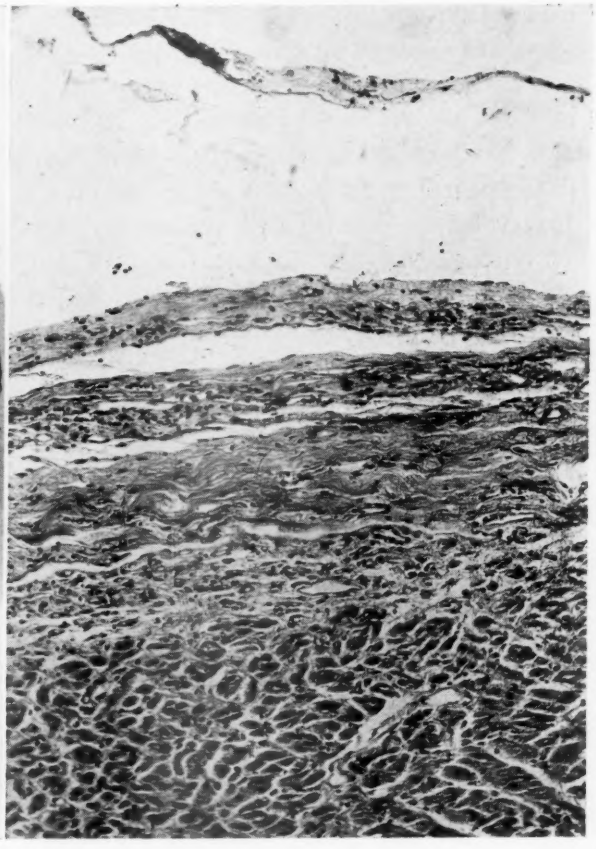

Fig. 7.

Figs. 6 and 7.—The heart of a man, aged 50 years (L-2; Table I). Sixty-three days after cardiac arrest and massage, fibrous pericarditis roughened the epicardial surface. Microscopically, the epicardium is somewhat thickened and sparsely infiltrated with lymphocytes, plasma cells, and large mononuclear cells.

C. G., a 50-year-old white man (L-2), was admitted to the Veterans Administration Hospital, Houston, Tex., for the treatment of pulmonary tuberculosis. Soon after admission he began to have cramping abdominal pain and distention and was treated by nasogastric suction without relief. Laparotomy disclosed a perforation of the ileum by a tuberculous ulcer. The portion of ileum was resected and anastomosed end-to-end. During the operation, 1 hour and thirty-five minutes after spinal anesthetic was given, cardiac arrest occurred. The abdominal incision was lengthened and the pericardium was opened through the diaphragm. The heart was in diastole and was flabby, therefore 1 c.c. of 1:1000 Adrenalin was injected

into the left ventricle and massage was started. Vigorous heart action was resumed almost immediately. However, the patient remained comatose with decerebrate rigidity and died sixty-three days after operation. Necropsy (N-71-53) revealed obliteration of the pericardial cavity by adhesions. The epicardial surface was rough and lusterless (Fig. 6). Microscopically the epicardium was thickened and sparsely infiltrated with lymphocytes, plasma cells and large mononuclear cells (Fig. 7). Associated findings revealed acute and chronic peritonitis with perforation of the ileum, ileitis, and pelvic abscess. There were extensive bilateral pulmonary tuberculosis and a caseous tubercle in the cerebellum.

COMMENT

Since the report of Tuffier and Hallion in 1898,[8] the clinical features of cardiac arrest have received a great deal of attention, but there has been little apparent interest in the effects of massage on the heart. Myocardial damage resulting from cardiac massage was observed by Thoma[7] and hemorrhagic pericarditis has also been described.[2] Myocardial rupture during manual compression has been reported by Hurwitt,[4] Haight,[1] Lam and associates,[6] and Hosler.[3]

According to these reports, and in our experience, cardiac massage is followed by an immediate, traumatic, hemorrhagic pericardial effusion. The effusion persists for at least ten days and is followed by an outpouring of inflammatory cells and fibrin so that the pericardial fluid becomes turbid with organization and fine fibrous adhesions. This reaction may progress to adhesive pericarditis.

It appears that the myocardial damage is in direct proportion to the duration of massage and is aggravated by previous myocardial changes. As a result of prolonged or too vigorous massage, there are epicardial hemorrhage and extravasations of erythrocytes between the myocardial fibers. If these traumatic myocardial changes occur in a heart already damaged by ischemia, rupture may ensue.

In all instances where massage lasted more than fifteen minutes there was evidence of some damage to the myocardium and pericardium. On the other hand, pericardial reaction, noted in nine cases, developed irrespective of the duration of massage and was not confined to cases in which the pericardium had been opened. It is likely that manipulation of the heart and intracardiac injection of various agents are sufficient to produce pericarditis. No conclusions can be drawn from the use of the defibrillator in regard to cardiac damage, for in four of the five cases in which it was used there was also prolonged massage and the changes are attributed to this factor.

Since cardiac massage is usually initiated hurriedly, manipulation tends to be vigorous and when massage is continued beyond fifteen minutes serious injury may follow. On the other hand, it may be prolonged safely if performed carefully. In an experimental study of cardiac arrest, Kay[5] massaged the hearts of 72 dogs from three to sixty-two minutes with damage to only one.

SUMMARY

Structural changes observed in the hearts of 14 patients who were treated by cardiac massage for cardiac arrest are reported. The reaction of the pericardium was a progressive pericarditis independent of the duration or technique

of massage. When the massage was prolonged over fifteen minutes the myocardial damage was moderate to severe. Rupture of the myocardium occurred in one instance after ninety minutes of massage.

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EVALUATION OF THE VARIOUS OPERATIVE METHODS FOR TOTAL GASTRECTOMY

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TOTAL gastric resection has become an easier procedure for surgeons and its operative risk has been diminished greatly due to improvements in operative technique, selective anesthesia, and the employment of antibiotics. The ideal or preferred operative method has not been established; there is continued confusion in the minds of surgeons as to which operative method should be selected for their particular cases. The known postoperative difficulties, such as agastric anemia, loss of weight, and dumping syndrome or stricture of the esophageal remnant, have been so great in the past that the impulse often is present to perform palliative procedures rather than the radical attempt to cure.

During the past ten years we have performed approximately 350 total gastric resections by applying three different operative methods as illustrated herein. We were able to pursue follow-up studies on all patients for purposes of statistical analysis. The purpose of this paper is to present an evaluation of the various operative methods we have employed.

TABLE I. TOTAL GASTRECTOMY: DIAGNOSIS OF CASES (FROM JANUARY, 1946, TO NOVEMBER, 1955)

CLASSIFICATION	NUMBER
Cancer	329
Ulcer	14
Total	343

OPERATIVE METHODS

For the convenience of this presentation, we have divided our three main operative methods as follows: (1) direct esophagoduodenostomy, (2) transplantation of an intestinal loop (jejunum) between the esophageal and duodenal remnants, and (3) esophagojejunostomy.

Esophagoduodenostomy After Removal of Total Stomach.—As Judd[5] has recently reported, this operative method affords a favorable postoperative state because the intaken food passes through the duodenum to accumulate many ferments and other digestive elements. However, this operative method can be employed only when the malignant tumor does not extensively involve the esophagus or when the mobilization of the duodenum is easy, so that the duodenal stump can be mobilized sufficiently to be approximated with the

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esophageal remnant. It has been well known that the distal end of the esophagus is resectable with the stomach by an abdominal approach when the infiltration of the lesion is limited within the abdominal esophagus.

A mobilization of the lateral aspect of the duodenum with the aid of traction sutures between the pancreatic head and the crura of the diaphragm (Fig. 1) allows direct esophagoduodenostomy in all cases, if the two conditions described above are preserved. This direct anastomosis is impossible when the cancer requires higher resection of the esophagus through a combined abdominothoracic incision. One hundred and fifty-four patients have been operated upon by this method since 1947 in our Department of Surgery and only five hospital deaths were experienced. The operative mortality rate therefore was 3.2 per cent.

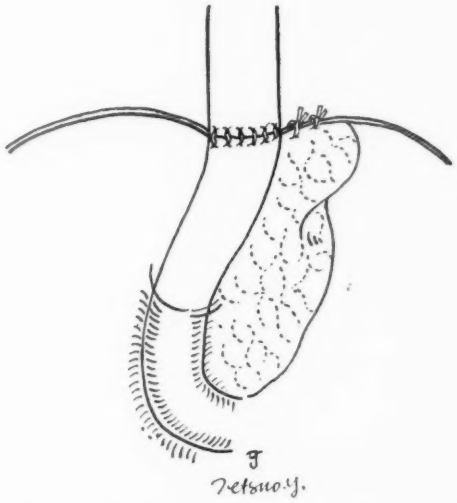

Fig. 1.—With traction sutures between the diaphragmatic crura and head of the pancreas.

Transplantation of Various Intestinal Loops Between the Esophageal and Duodenal Remnants.—This operative method is complex in its technical execution and therefore constitutes a greater ordeal for the patient, but the postoperative continuity of the alimentary tract is more physiologic than in the others because the transplanted loop partly substitutes for gastric function and the passage of the food is always through the duodenum. Our predecessor, Professor Seo, attempted this operative method in 1935, and reported the procedure as "Physiological total gastric resection." Longmire[8] has recently repeatedly reported this transplantation of a transected jejunal loop to be the most ideal method for total gastric resection. Although it requires a more complicated operative technique, this procedure is advantageous when invasion by the cancer is quite high into the esophagus and necessitates the resection of an appreciable length of the esophagus for the radical eradication of the cancer. A sufficient length of jejunal loop can be resected as desired and be transplanted between the thoracic esophagus and the duodenum. We have operated upon thirty-seven patients in the employment of this jejunal transplantation method and only one hospital death has been experienced.

Esophagojejunostomy After Total Removal of the Stomach.—Esophagojejunostomy is the most popular method of reconstruction after total gastrectomy. One great disadvantage of this operative method is that the re-established alimentary continuity does not allow the passage of the food through the

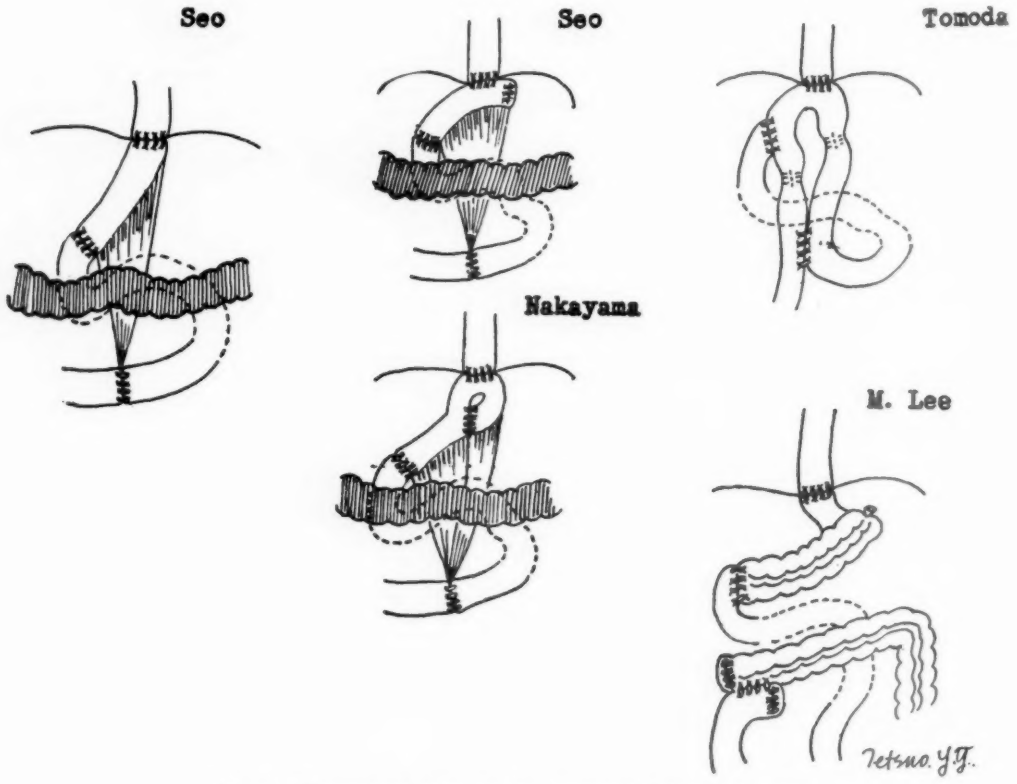

Fig. 2.—Transplantation of the resected intestinal loop.

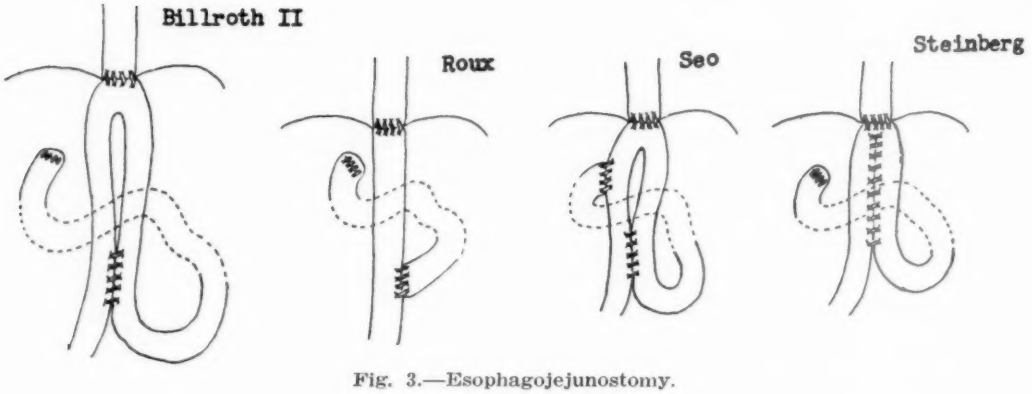

Fig. 3.—Esophagojejunostomy.

duodenum. This results in the many postoperative syndromes which have been reported previously from several sources. We have performed this type of anastomosis in 125 patients since 1947.

TABLE II. OPERATIVE RESULTS: TOTAL GASTRECTOMY (FROM JANUARY, 1947, TO NOVEMBER, 1955)*

OPERATIVE METHOD	NUMBER OF CASES	HOSPITAL DEATHS	MORTALITY RATE (%)
Esophagoduodenostomy (end to end)	154	5	3.2
Transplantation of the jejunum	37	1	2.7
Esophagojejunostomy	125	3	2.9
Total	316	9	2.84

*Except 27 cases operated upon by previous Nakayama method.

TECHNICAL PROBLEMS

For the routine total gastric resections, a midline incision from the xyphoid process to the umbilicus is employed. This incision, however, can be extended into the left thorax, if the lesion requires a higher resection of the esophagus.

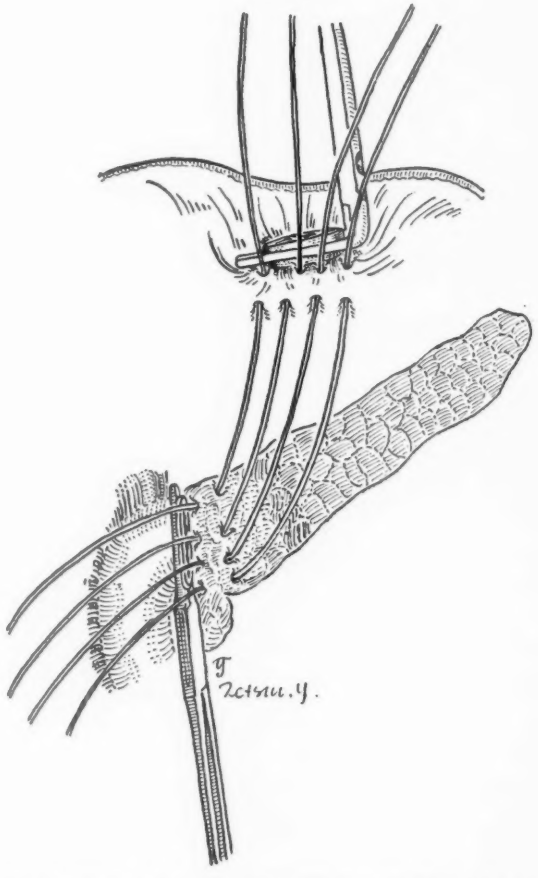

Fig. 4.—Traction sutures between the pancreatic head and the diaphragmatic crura at the posterior aspect of the esophageal remnant.

Traction Sutures.—To avoid undue tension on the anastomosing site, particularly when esophagoduodenal direct anastomosis is attempted, traction sutures between the serosa of the pancreatic head and the fascia of the diaphragmatic crura are placed before the anastomosis is performed. Their dual

purpose is not only to reduce the tension on the anastomosis, but also to approximate both remnants by simple manipulation. For the esophagojejunostomy this traction suture is placed between the posterior aspect of the jejunal serosa and the crura of the diaphragm. If the anastomosis is performed within the thoracic cavity, the traction sutures are applied between the mediastinal pleura and the posterior wall of the intestinal loop to be anastomosed with the esophagus.

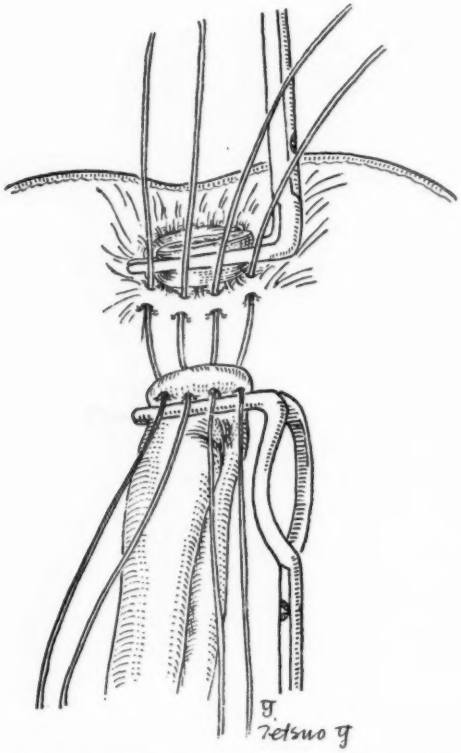

Fig. 5.—Fixation of the jejunal posterior wall with the diaphragmatic crura at the posterior aspect of the esophageal remnant.

Anastomosis.—Two layers of sutures are always employed for the esophagoduodenal or esophagojejunal anastomoses. Due to the fact that the esophagus lacks a serosal coat, the outer layer sutures are placed between the serosa of the intestinal loop and the diaphragmatic crura to wrap over the anastomotic site. A musculoserosal suture is not preferable, especially for the anterior anastomosis. For the inner layer, a tight through-and-through Albert's suture is indicated. Suture between the outer surface of the esophagus and the serosa of the intestinal loop (musculoserosal suture) is not sufficient to prevent a leakage from the anastomosis.

With the help of the traction sutures and the anastomosing technique as described above, we have been able to prevent many postoperative deaths during hospitalization due to leakage from the anastomoses. A summary of the cases operated upon and their operative results is illustrated in Table II.

POSTOPERATIVE COURSE OF TOTAL GASTRECTOMY PATIENTS HAVING ANASTOMOSES BY DIFFERENT OPERATIVE METHODS

There is not so much difference among these 3 methods as far as the duration of hospitalization and the degree of postoperative shock are concerned.

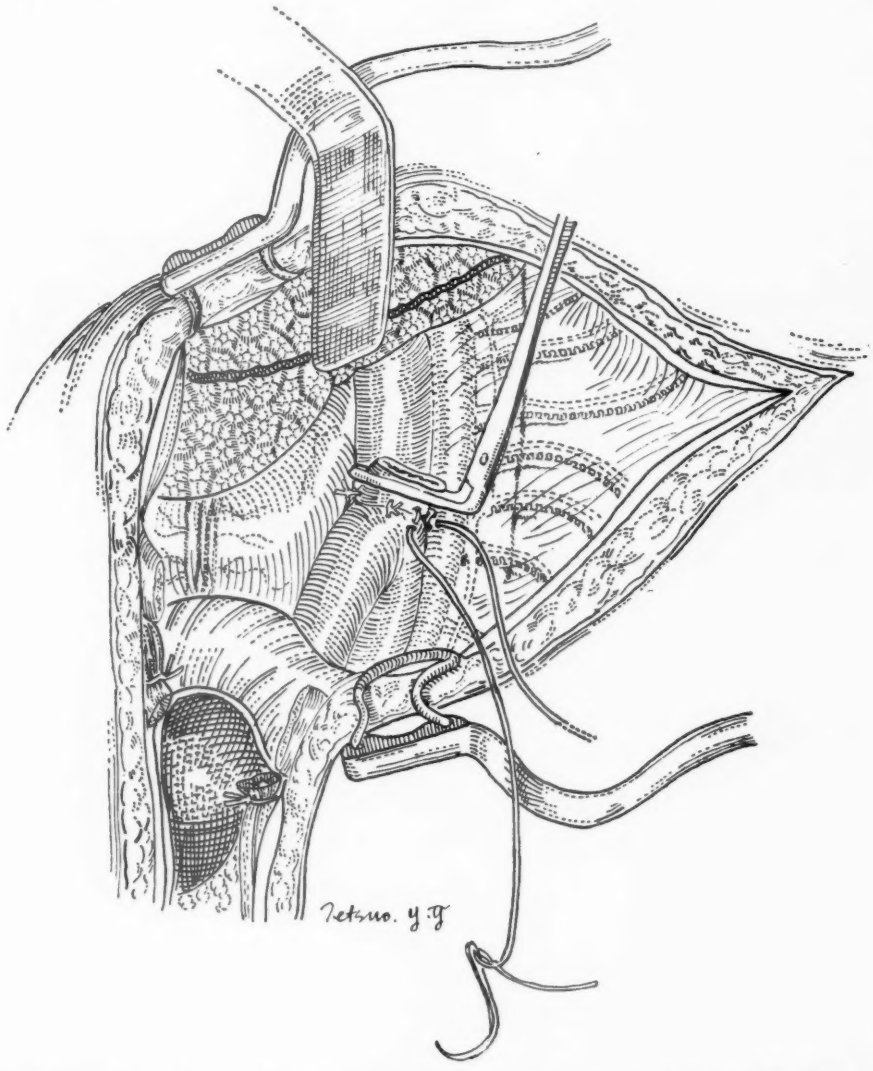

Fig. 6.—Additional traction sutures between the jejunal serosa and the mediastinal pleura.

Evaluation Based on Clinical Laboratory Examinations During the Operation and the Postoperative Course.—

Amount of bleeding: Esophagoduodenostomy entails the least amount of bleeding during the operation, and the intestinal transplantation method is accompanied by the most bleeding. However, the quantitative difference in bleeding in the average patient is too small to criticize the methods as illustrated.

Liver function tests: Comparative study of the liver function tests (B.S.P.), hippuric acid, serum cobalt, and cadmium tests, etc., after total gastric re-

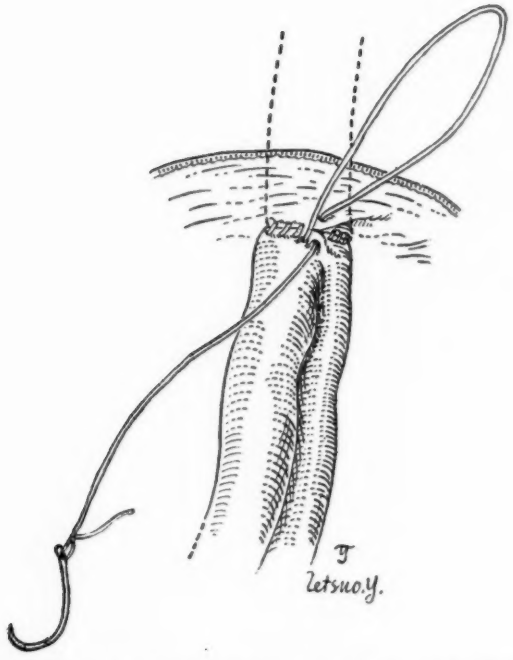

Fig. 7.—The continuous seroserosal suture between the jejunal anterior wall and the diaphragmatic crura at the anterior aspect of the esophageal remnant.

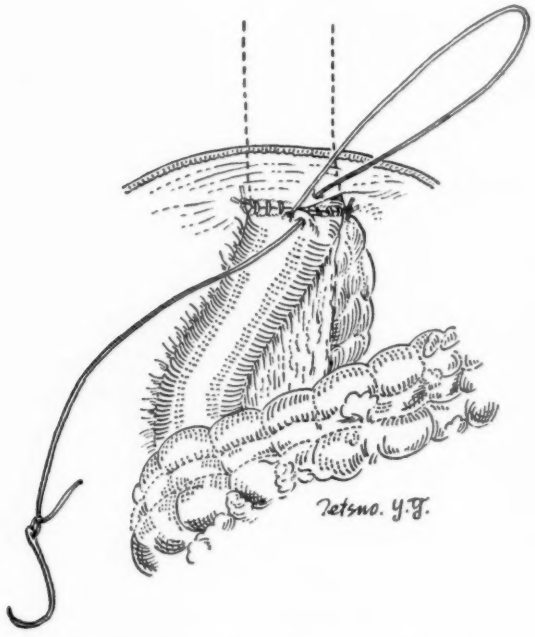

Fig. 8.—Anterior continuous seroserosal suture between the duodenum and diaphragmatic crura.

sections revealed that the influence on liver function due to the various operative stresses was minimum in the esophagoduodenostomized cases. All patients showed a slight impairment of liver function one year after the operations. Those patients in whom the jejunum was transplanted have shown the most

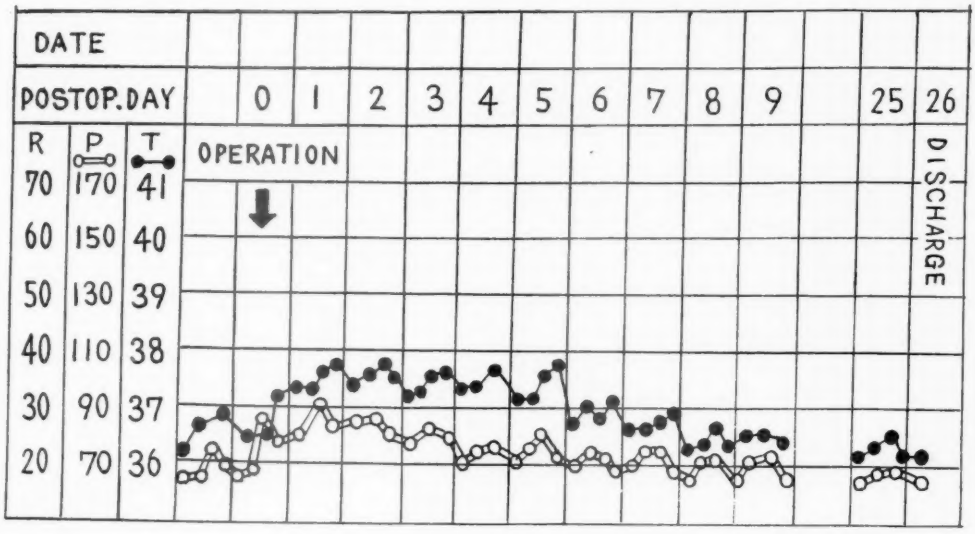

Fig. 9.—Total gastrectomy and esophagoduodenostomy (end to end)— (average).

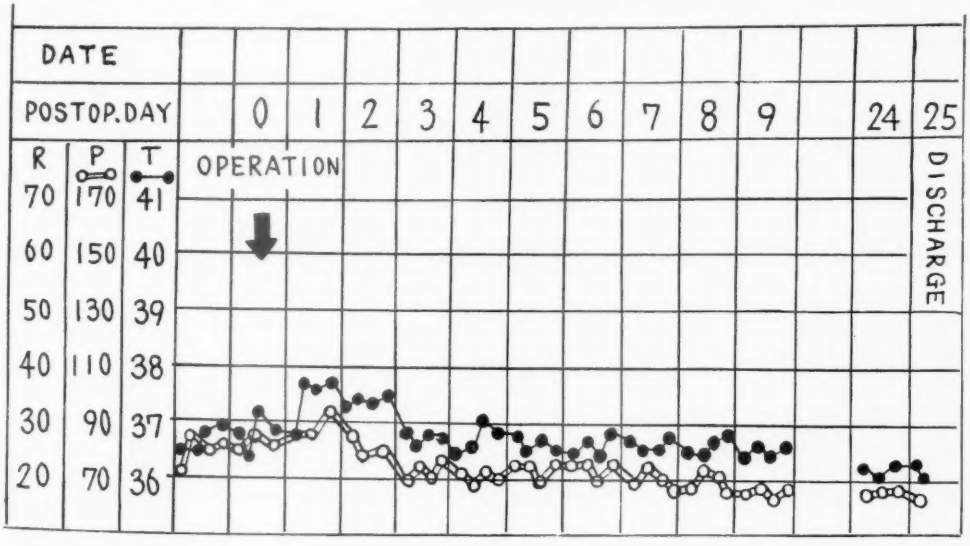

Fig. 10.—Total gastrectomy and transplantation of the jejunum (average).

satisfactory recovery of their liver functions four weeks after the operations, although the slowest recovery also is found among these cases. Esophagojejunostomy results in the least satisfactory recovery.

Postoperative Complaints.—

Dysphagia: The most miserable complaint after total gastric resection is dysphagia. Dysphagia is due mostly to the stricture of the anastomosis and

usually is caused by two conditions. One is a recurrence of the carcinoma at the site of anastomosis and the second is a cicatricial stricture of the anastomosis. It occasionally happens that the operator notices an unexpectedly

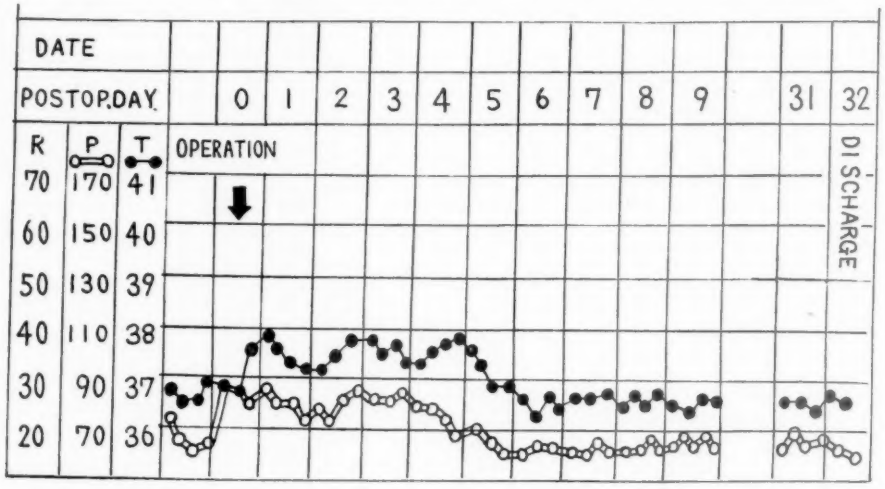

Fig. 11.—Total gastrectomy and esophagojejunostomy (average).

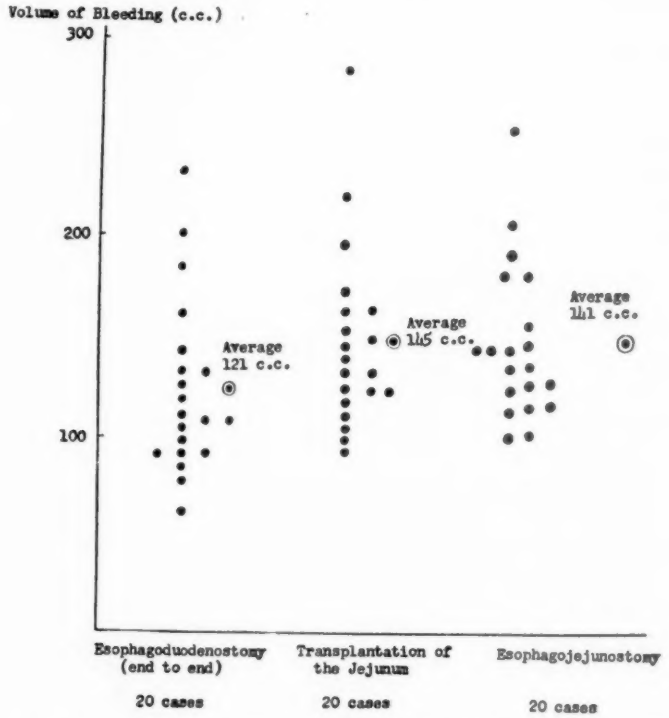

Fig. 12.—Volume of bleeding during operation (total gastrectomy).

high invasion by the malignant growth at the time he is scheduled to perform the operation by an abdominal approach. When the general condition of the patient is not good enough to tolerate the greater operative stress of a

thoracotomy, an intra-abdominal esophagoduodenal or esophagojejunal anastomosis is performed for palliation. The frequency of postoperative stricture of the anastomosis is partially because of these palliative operations. About half of our patients having esophagoduodenostomies have returned to our clinic four to six months postoperatively complaining of difficulties in swallowing. In our experience the incidence is higher in those patients who had relatively high resections entirely within the abdomen and without any incision

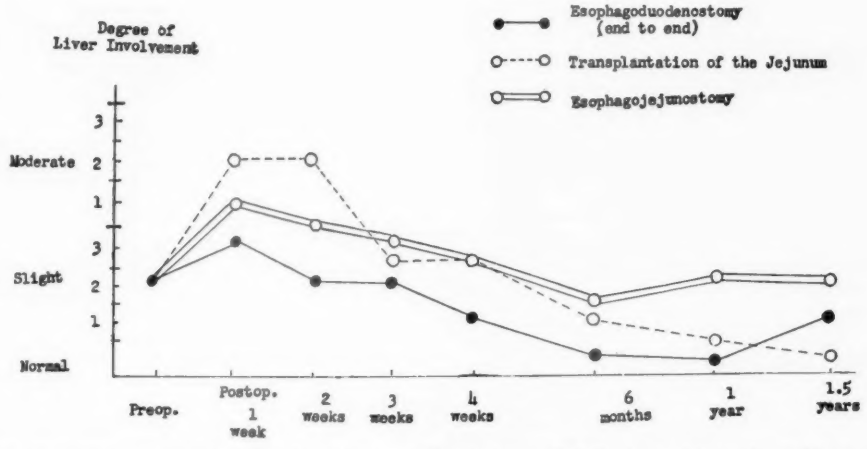

Fig. 13.—Transition of liver function. Judged from B.S.P. test, hippuric acid, serum Co and Cd reaction.

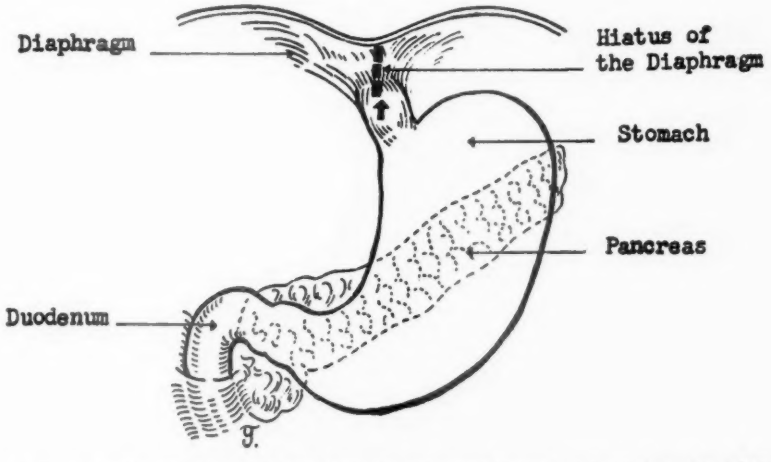

Fig. 14.—The arrow indicates the incision line to the esophageal hiatus for the higher resection of the lower esophagus.

of the diaphragm. A vertical incision of the diaphragm always should be performed to avoid the postoperative stricture at the anastomosed site for the purpose of not only obtaining a wider operative visualization but also to widen the hiatus. The transplantation method has brought the least of this complication (Table III).

TABLE III. TOTAL GASTRECTOMY: FREQUENCY OF POSTOPERATIVE STENOSIS OF ANASTOMOSIS SITE (CASES SURVIVING LONGER THAN SIX MONTHS)

OPERATIVE METHOD	CASES FOLLOWED UP	+	-
Esophagoduodenostomy (end to end)	37 patients	16 (43.3%)	21 (56.7%)
Transplantation of the jejunum	18	2 (11.1%)	16 (88.9%)
Esophagojejunostomy	16	5 (31.8%)	11 (62.5%)

Postoperative esophagitis: Heart burn after total gastric resections is mostly caused by regurgitation of the bile into the esophageal remnant. These complaints are found most commonly in the patients with esophagoduodenostomies and least frequently in patients with a transplanted jejunum (Table IV). The complaints often can be relieved by advising the patient to take some acid solution or acid-containing foods.

TABLE IV. TOTAL GASTRECTOMY: HEARTBURN (CASES SURVIVING LONGER THAN ONE YEAR)

OPERATIVE METHOD	CASES FOLLOWED UP	NUMBER AND PER CENT OF HEARTBURN
Esophagoduodenostomy (end to end)	29	17 (58.6)
Transplantation of the jejunum	6	0 (0)
Esophagojejunostomy	6	2 (33.3)

Diarrhea: Diarrhea is found most frequently in patients with esophagojejunostomies (one-third of the entire operated cases), and has never occurred in patients with transplanted jejunum (Table V).

TABLE V. TOTAL GASTRECTOMY: DIARRHEA (CASES SURVIVING LONGER THAN ONE YEAR)

OPERATIVE METHOD	CASES FOLLOWED UP	NUMBER AND PER CENT OF DIARRHEA
Esophagoduodenostomy (end to end)	29	3 (10.3)
Transplantation of the jejunum	6	0 (0)
Esophagojejunostomy	6	2 (33.3)

Dumping syndrome: The frequency of this syndrome after the operation has been carefully studied in our clinic. In general we found that the patients with transplanted jejunum enjoyed the best reconstructed alimentary tract. More than one-third of the esophagojejunostomized patients have come back to the clinic with some symptoms referred to this syndrome. However, these complaints are not severe enough to interfere with the daily livelihood of the patients.

TABLE VI. TOTAL GASTRECTOMY: POSTPRANDIAL SYNDROME (CASES SURVIVING LONGER THAN ONE YEAR)

OPERATIVE METHOD	CASES FOLLOWED UP	NUMBER AND PER CENT OF SYNDROME
Esophagoduodenostomy (end to end)	29	4 (13.8)
Transplantation of the jejunum	6	0 (0)
Esophagojejunostomy	6	3 (33.3)

Agastric anemia: This complication has been one of the biggest problems among surgeons who have performed total gastric resection. The manner of re-establishment of alimentary continuity greatly influences this type of anemia. What is the cause of this complication? In our opinion, the operative technique is the best prevention of agastric anemia.

All of our patients who have survived longer than three years after the operation have been carefully studied. We have had no patients with anemia severe enough to be called pernicious, but there are some patients who have suffered from a moderate degree of anemia after the operations. Anemia is more pronounced in those cases who had esophagojejunostomy. The cause of such anemia has been investigated and is believed to be an insufficient absorption of iron, most probably due to lack of passage of the food through the duodenum, when the alimentary tract is reconstructed in such a way.

DIGESTIVE AND ABSORPTIVE ABILITY OF THE RECONSTRUCTED TRACT

Absorption of carbohydrates, fats and proteins has been greatly impaired in the gastrojejunostomized cases.

LOSS OF WEIGHT

The transplantation method achieved the best results in gain of weight after the operation.

SURVIVAL RATE

Total gastric resection should be avoided for the treatment of the benign lesions such as ulcer, because of (1) its extensive surgical stress, and (2) the various postoperative physiologic disturbances due to lack of the stomach. Hence, the objective of total gastrectomy is solely the treatment of malignant tumors and mostly of very extensive gastric cancers.

TABLE VII. TOTAL GASTRECTOMY: INFLUENCE UPON THE BODY WEIGHT (CASES SURVIVING LONGER THAN ONE YEAR)

OPERATIVE METHOD	CASES FOLLOWED UP	GAIN	NO CHANGE	LOSS
Esophagoduodenostomy (end to end)	29	14 (48.2%)	11 (37.9%)	4 (13.8%)
Transplantation of the jejunum	6	5 (83.3%)	1 (16.6%)	0 (0%)
Esophagojejunostomy	6	3 (50.0%)	2 (33.3%)	1 (16.6%)

TABLE VIII. SURVIVAL RATE OF THE TOTAL GASTRECTOMIZED PATIENTS (FROM JANUARY, 1946, TO JUNE, 1953)

Cases operated upon	176
Cases followed up	157
Six months	69.4%
One year	34.3%
One and one-half years	25.0%
Two years	18.8%
Three years	15.8%

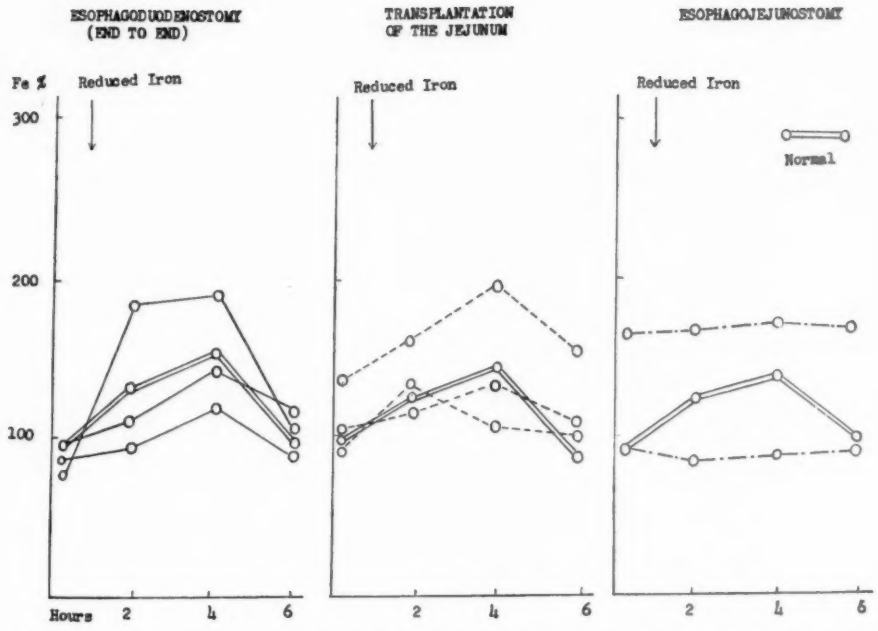

Fig. 15.—Iron adsorption curve (more than one-year survivors after total gastrectomy).

OPERATIVE METHOD	PROTEIN %	FAT %	GLUCIDES %
ESOPHAGODUODENOSTOMY	85.8	93.8	99.2
TRANSPLANTATION OF THE JEJUNUM	85.3	93.3	98.7
ESOPHAGODUODENOSTOMY	80.3	78.4	98.1

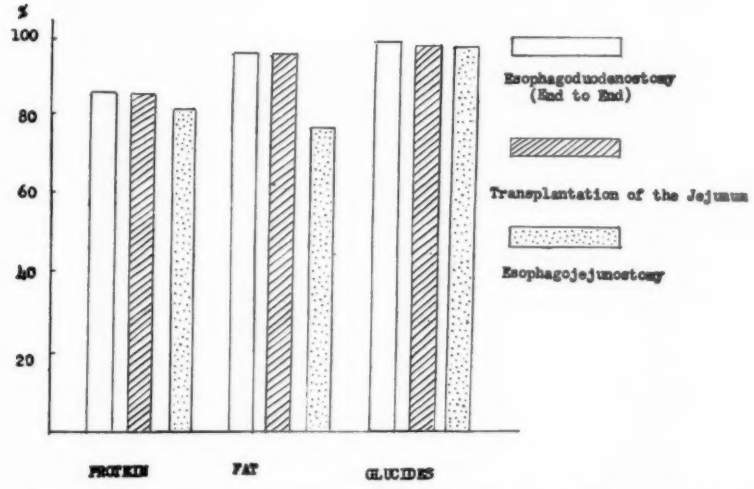

Fig. 16.—Digestion and adsorption (1 to 5 years after total gastrectomy).

Hence, recurrence rate of cancer after total gastric resection is relatively high. Esophagoduodenostomy has been performed successfully for palliative purposes, as described previously, however, the recurrence rate of this operative method is higher than for other procedures. Esophagojejunostomy also has been performed for those patients who had developed metastases in the head of the pancreas or to the base of the liver. The survival rate three years postoperatively was 15.8 per cent (Table VIII). Total gastric resections are not

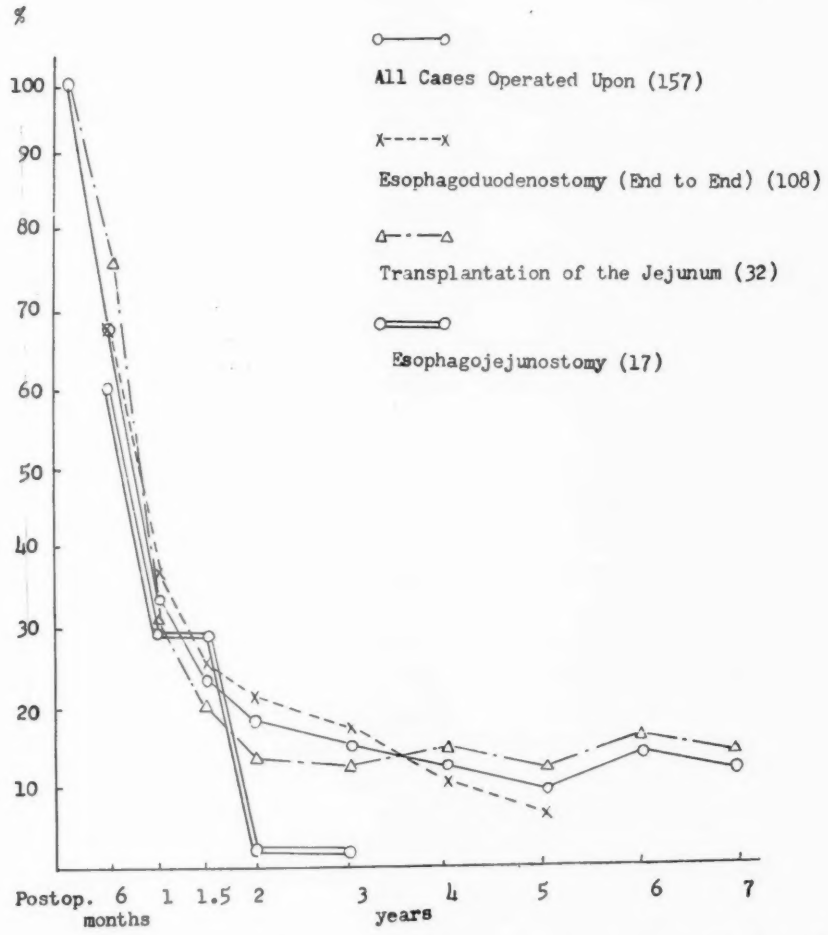

Fig. 17.—Percentage of survivors after total gastrectomy (from January, 1947, to December, 1953).

performed in our clinic in the treatment of small cancers in the pyloric region or antral portion. The postoperative survival rate has been studied comparatively according to these three operative methods of restoration as illustrated in Fig. 17. The method of transplanting the jejunum afforded the best survival rate because this operative method was selectively performed in those patients for whom complete eradication of the cancers was attempted.

CONCLUSIONS

Evaluation of operative methods for total gastric resections in the treatment of gastric carcinoma have been based on approximately 350 total gastrectomies performed in our clinic since 1947.

1. Esophagoduodenostomy after the total removal of the stomach is technically the easiest of three main operative methods and results in a minimal degree of operative stress.

2. Various clinical investigations performed on certain patients after the operations revealed that the minimal operative stress and the most prompt recovery occurred in the esophagoduodenostomized cases. However, this method is not applicable when the lesion infiltrates the esophagus.

3. Postoperative stricture at the site of the anastomosis is observed most frequently after esophagoduodenostomy. Careful operative technique is required to avoid stricture.

4. Agastric anemia is found most frequently in the esophagojejunostomized patients. This is due to passage of the food by detouring the duodenum.

5. Digestive and absorptive ability of the nutritive elements are maintained more sufficiently in the operation with jejunal transplantation.

6. The postoperative survival rate is about the same by all methods. It is our belief that transplantation of the resected intestinal loop between the esophageal and the duodenal remnant is the preferable operative method if the general condition of the patient is good enough to tolerate such severe operative stress. Esophagojejunostomy is considered to be the most unfavorable procedure according to our investigations.

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A TECHNIQUE FOR THE REVERSIBLE EXCLUSION OF THE LIVER IN DOGS

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EXPERIMENTAL studies on hepatectomized dogs have been hampered considerably by the fact that the mortality of the procedure even in skilled hands is frequently over 50 per cent. Air embolus and shock from hemorrhage are the two major contributors to this mortality.

The liver is a unique organ inasmuch as it has two blood supplies. The portal vein supplies the majority of blood to the liver. The hepatic artery supplies its systemic flow. However, ligation of the portal vein does not affect the blood supply to the liver alone. Since the portal vein drains the entire intestinal and splenic areas, its ligation causes a complete cessation of flow from these sites, the resultant clinical picture is similar to that seen with mesenteric vein thrombosis. Under such circumstances, the arterial supply to the splanchnic area is intact. However, the blood finds no escape route because of the venous blockage. A regional hypertension ensues with actual bleeding into the intestines and eventual shock of the organism from lack of effective circulating blood volume. Any procedure, therefore, which attempts to remove the liver must re-establish the portal circulation in order to ensure survival.

A one-stage hepatectomy would certainly be superior to the two-stage procedure providing the mortality could be lowered. Leveen and Lewis[2] devised a plasticized vinyl tubing adapted after the glass cannula used in the one-stage hepatectomy as described by Firor and Stinson[1] (Fig. 1). The use of this flexible tubing eliminated to a considerable extent many of the difficulties encountered with the rigid glass cannula in by-passing the liver. According to Leveen and Lewis "the difficulties in the one-stage method of Firor and Stinson arise from the use of a cannula which is rigid and cannot be occluded by clamping during its insertion. Hemorrhage and air embolization are unavoidable operative catastrophies. A flexible cannula could be more easily manipulated . . . easier to introduce into the vena cava . . . (and) obviate the danger from hemorrhage and air embolization."

The liver in the dog is unique in that its immediate drainage is not accessible to surgical ligation per se. In the dog many lobes of the liver empty directly into the vena cava without forming any vascular channels. It becomes necessary, then, if one desires to remove the liver from the circulation, or

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perform a total hepatectomy, to utilize a method for occluding the hepatic veins. A long tube inserted into the vena cava, before it enters the liver substance, extending above the diaphragm is necessary (Fig. 2). Secure

Fig. 1.—Flexible plastic cannula as described by Leveen and Lewis.

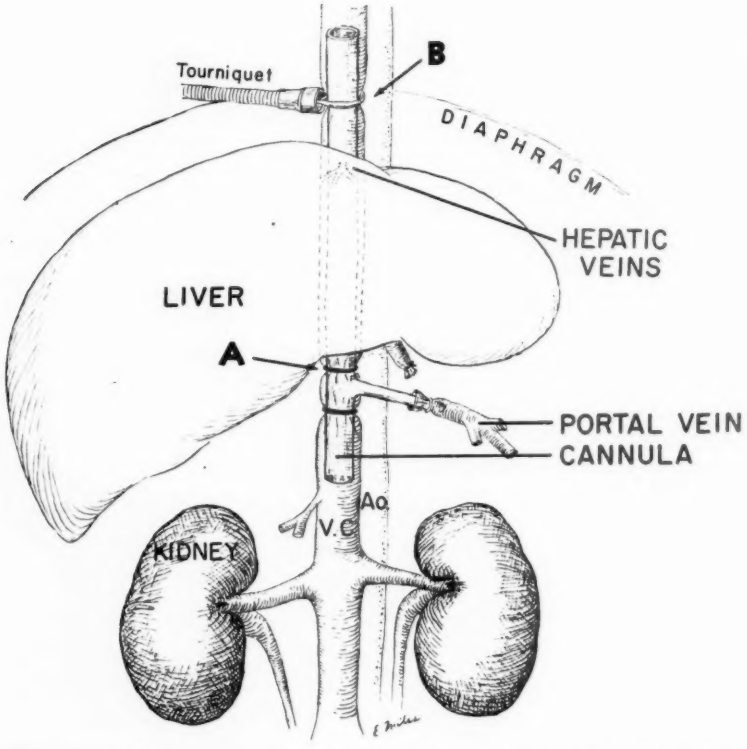

Fig. 2.—A diagrammatic representation of the tube inserted into the venous circulation. Hepatic drainage trapped between ligatures *A* and *B*.

ligatures compressing the vena cava against the cannula, both proximal and distal to the liver, serve to occlude the hepatic venous drainage completely while the caval flow is unimpeded through the central portion of the tube. Anastomosis of the side arm of the cannula to the portal vein short-circuits the portal blood into the caval circulation or, in effect, produces a direct Eck fistula.

It occurred to us that by means of this ingenious plastic tube we might be able not only to remove the liver from the dog's circulation but also, by use of tourniquets, to replace it as desired. After a prolonged period of trial and error, the following technique was devised with considerable success.*

TECHNIQUE

It soon became apparent that many details of the operation were important if its success was to be ensured. The plastic T-tube was treated with Dessicote several hours before the anticipated surgical procedure and permitted to dry thoroughly so as to prevent any possibility of blood clot formation. With the operation as presently described, one assistant was adequate; however, when available, a second assistant facilitated the procedure. A right thoracoabdominal approach proved to be much superior to the abdominal incisions, although adequate exposure could be obtained with the latter with some difficulty. Endotracheal oxygen with intermittent positive pressure is used. Anesthesia consists of preoperative sedation with morphine sulfate and the intravenous administration of Serutal, which is allowed to drop as needed.

A long midline incision is extended to the ensiform process, at which point the incision takes an oblique turn to enter the seventh or eighth intercostal space. This incision in the midline gives rise to a minimum of bleeding. The costal cartilages are divided. The diaphragm is then divided between clamps down to the vena cava. All bleeders are ligated. A self-retaining retractor is inserted in the abdomen along the costal cage on the right and the upper aspect of the midline incision on the left. The duodenum is identified and elevated into the wound. The abdominal viscera are then packed to the left of the duodenal mesentery which acts as a large towel in packing off the abdominal organs. The vena cava is clearly identified and exposed. The adventitia of the vena cava is carefully stripped away, from the right kidney to a point where it enters the liver. Ordinarily there are no small veins to be found communicating with the vena cava in this area except for the adrenal veins and an occasional lumbar vein. The latter must be ligated and divided carefully. The right adrenal vein in particular may give some difficulty as it is quite adherent and requires care in dissection. We have not found it necessary to sacrifice the left adrenal vein and, on occasion, in larger dogs, have been able to work satisfactorily leaving even the right adrenal intact. A heavy ligature of silk or cotton is then passed beneath the vena cava just above the right kidney and another just below the liver. A clamp is placed about the narrow arm of the plastic T-tube. A second hemostat occludes the

*Particular acknowledgment is extended to Mr. Charles Jacobs, laboratory assistant, for his invaluable assistance.

main cannula at the junction of the short segment to the small side arm. At this point, the surgeon and his assistant are alerted, for the following procedures will completely occlude the vena cava and minimum time should lapse before their completion.

The assistant makes firm traction on the ligature placed about the vena cava just as it enters the liver. A nonerushing arterial clamp is then placed about the vena cava distal to the site of the ligature about the vein, just above the kidneys. A 1 cm. transverse incision is made into the vena cava by means of a scissors at least 2 cm. proximal to the renal vein. The transverse incision is bisected in longitudinal fashion and extended proximally for a distance of 0.5 cm. The long arm of the T-tube is then inserted without difficulty rapidly into the vena cava in a cephalad direction, to the point where the side arm reaches the limits of the incision in the vein (Fig. 3). The proximal ligature is tied securely about the vena cava and the main trunk of the cannula. The short end of the T-tube is then inserted into the distal portion of the vena cava through the same incision. This is facilitated by the flexibility of the cannula. The second strong ligature is securely tied about the distal vena cava over the shorter limb of the tube. It is important that this portion of the cannula is short enough so as not to occlude the renal veins. The arterial clamp is then promptly removed, as is the hemostat, from the main trunk of the cannula, and blood can be seen coursing through the vena cava. This entire procedure should take no more than three to four minutes and should entail a loss of no more than 5 to 10 c.c. of blood.

The portal vein is then isolated and dissected free of its adventitia from the hilum of the liver distally for at least 4 cm. One constant branch, the pancreaticoduodenal vein, is sacrificed. It is not necessary to divide the splenic vein. At this point action must again be deliberate, since the subsequent procedures will be performed while the portal vein is occluded. A nonerushing arterial clamp is placed about the portal vein at its most distal dissection. The portal vein is then divided and ligated proximally at the porta hepatis (Fig. 4). The lumen of the distal portion of the portal vein is placed over the side arm of the T-tube and a ligature firmly fixes this in situ. The nonerushing arterial clamp is then removed as well as the hemostat from the side arm of the cannula, and portal venous blood is seen to course through (Fig. 5). We have not found it necessary in the course of our experiment to use heparin either in the tube or in flushing out the veins as long as the Dessicote was properly applied preoperatively. The time during which the portal vein is clamped should not exceed three to four minutes. The blood loss should be under 5 c.c.

The common hepatic artery is then identified and isolated from surrounding structures and clamped. In acute experiments, the entire hepatoduodenal ligament including the biliary structures is divided between clamps and ligated with the exception of the hepatic artery. This step, while not necessary, is advisable because of the many collaterals which arise in the gastrohepatic ligament and serve to feed the liver through anastomotic channels. This maneuver also insures the complete denervation of the liver.

Fig. 3.

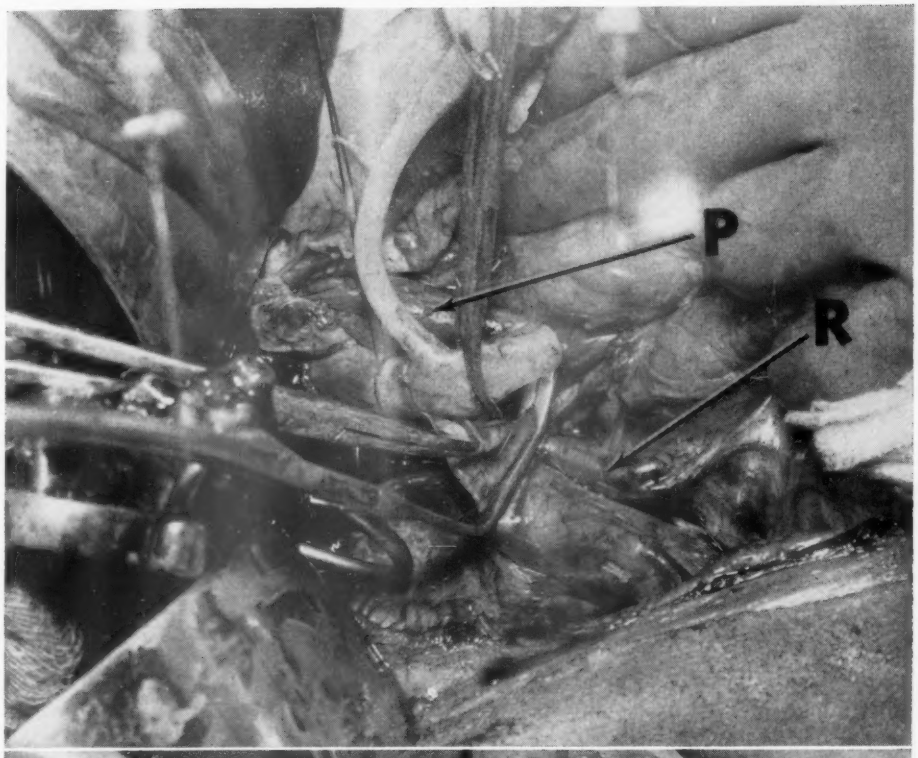

Fig. 4.

Fig. 3.—The long arm of the cannula has been inserted in a cephalad direction into the vena cava. A stout ligature about the vena cava secures it. A noncrushing clamp occludes the distal vena cava (and renal veins) prior to the insertion of the short arm of the tube. *P*, Portal vein; *R*, left renal vein.

Fig. 4.—The main limb of the cannula is secured in place in the vena cava. The side arm is being inserted into the distal aspect of the occluded portal vein.

The liver is now rotated clockwise and to the left. A thin avascular mesentery will be noted connecting the right lobe of the liver to the diaphragm. This is incised. By means of blunt dissection posteriorly and utilizing palpation of the tube within the vena cava, a cleavage plane is readily established between the liver and the diaphragm behind the vena cava. A very stout ligature of cotton or silk is passed beneath the vena cava at this point. This ligature is placed within a Rumel tourniquet and the tourniquet is tightened so that the vena cava is occluded about the tube. Any possible remaining collateral circulation is removed by division of the left and right coronary ligaments which contain branches of the phrenicoabdominal arteries.

Fig. 5.—The completed experiment. The gall bladder may be seen in the left lower corner of the picture. The springlike steel substance in the left upper corner of the picture is a portion of the Rumel tourniquet. This compresses the vena cava about the tube between the liver and the diaphragm.

At this point the liver has been denervated and completely excluded from the dog's circulation. The resultant anoxia, if it persists for at least one hour, causes extensive hepatic necrosis. We have utilized such animals to investigate the role of the damaged liver in the genesis of shock. The significance of a bacterial factor, a vasodepressor substance (VDM), and hypovolemia have all been studied. Preliminary results indicate that local blood loss into the injured organ may reach significant proportions. The subsequent decrease in circulating blood volume appears to be the prime factor in the production of shock associated with hepatic necrosis.

The value of this experimental tool lies in the fact that the liver can be easily replaced within the circulation in a matter of minutes. It is necessary only to release the arterial clamp on the hepatic artery and loosen the tourniquet about the hepatic vein to revascularize the liver. The portal circulation may, if desired, be reconnected with great facility by means of a small plastic tube which has been suitably treated with Dessicote. This avoids the necessity of a suture anastomosis and takes but one to two minutes to complete.

SUMMARY

A method has been described by means of which the liver of a dog can be completely denervated and removed from the circulation as desired. Within minutes it can be returned to its normal place in the body's circulation. We have utilized this technique in 50 animals. The procedure has a low mortality—approximately 15 per cent—and needs no exceptional skill, once mastered. By means of this preparation we have been able to study the relationship of hepatic damage and shock. Preliminary results incriminate the loss of blood into the necrotic liver as the significant factor in the diminished circulating blood volume associated with shock. This experimental tool opens an entire field for the investigation of liver function not hitherto available.

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CARCINOMA OF THE ESOPHAGUS

Report of Cases: 1947 to 1953

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A GENUINELY effective treatment for malignant neoplasia of the esophagus continues to elude the medical profession. Occasionally we lose the patient in attempting to cure him, often we palliate him, but, unfortunately, in too few instances do we succeed in curing him. However discouraging the picture as a whole remains, we must continue to recognize that there are certain anatomic regions of the esophagus as well as biological types of tumors originating in this organ which lend themselves to successful eradication in a substantial number of cases. Our obligations to the cancer patient, however, should not be confined to our efforts to cure him. That we can give substantial palliation by resection in a fair percentage of cases, at certain levels more than at others, has already been established by others. Where cure may not be possible, palliation, therefore, should be our goal and this often is sufficient justification for a properly conceived and well-executed operation.

The authors have collected the material which follows from the Roswell Park Memorial Institute and the Buffalo General Hospital and have published it as a single report. The justification for this lies in the close relationship of these institutions from the point of view of geography, philosophy of treatment, and personnel. In a complementary sense it also represents the experience of two clinics each drawing its material from somewhat different social and economic levels of the community.

MATERIAL

All cases entering the above institutions between Jan. 1, 1947, through December, 1953, in which a positive histologic diagnosis of malignant neoplasm of the esophagus or cardia of stomach with invasion of the esophagus was made either before, during, or after surgery, are included here. The follow-up report notes the condition of the patient at the termination of 1953.

A total of 138 histologically proved carcinomas of the esophagus and cardia of the stomach comprise this report. Of this group, 111 were discovered in the esophagus itself and were histologically grouped as squamous cell carcinomas. Twenty-seven cases, although presenting obstructive symptoms and low in position, were histologically verified as adenocarcinomas. We have considered

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these to be carcinomas of the cardia. Except for the rather large percentage of lesions at mid-third level operated upon at the RPMI, the percentage of cases at each level corresponds with those already reported by others, there being a gradual increase in incidence when catalogued by levels from the cricoid toward the cardia.

LEVEL OF OCCURRENCE

TABLE I. BGH AND RPMI.* CARCINOMA OF ESOPHAGUS SERIES FROM 1947 TO 1953

LEVEL OF LESION	NUMBER OF CASES	
	BGH	RPMI
Cervical	7	4
Upper one-third	12	7
Middle one-third	17	38
Lower one-third	10	16
Cardia with esoph. exten.	12	15

Total: 138 diagnosed carcinoma of esophagus
111 cases; squamous cell; cervical to lower one-third (inclusive)
27 cases; adenocarcinoma; cardia with esophageal extension and obstruction

*Buffalo General Hospital and Roswell Park Memorial Institute.

AGE DISTRIBUTION

TABLE II. BGH AND RPMI. CARCINOMA OF ESOPHAGUS SERIES FROM 1947 TO 1953

DECADE	NUMBER OF PATIENTS	
	(RPMI)	(BGH)
40-50	4	4
50-60	26	19
60-70	31	19
70-80	19	16

While it is frequently stated that carcinoma has no age limit, it is also equally true that within this framework certain cancers have a sharp predilection for a particular period in life. The geriatricians tell us[1] that senesence begins at about 40 years of age. In the series reported here no patient with carcinoma of this organ was seen who had not passed his fortieth year. This is therefore in our experience a disease of the senesent period of life in the more technical sense of the term. An examination of Table II indicates only a few cases appearing in the fifth decade of life. From 50 until 80 years of age the distribution seems fairly uniform.

SEX INCIDENCE

TABLE III. BGH AND RPMI. CARCINOMA OF ESOPHAGUS SERIES FROM 1947 TO 1953

SEX INCIDENCE—NUMBER OF CASES OF CANCER OF ESOPHAGUS	
MALE	FEMALE
67 cases (RPMI)	13 cases (RPMI)
46 cases (BGH)	12 cases (BGH)

Many of the statistics reporting carcinoma of the esophagus give figures ranging from 4 to 1, to 8 to 1 preponderance in males. The figures herein reported indicate an incidence of only 4 to 1 male preponderance. The marked

dissimilarity in the geographical distribution of the patients and the varying economic levels of the case material represented in these separate clinics make the similarity of the sex incidence more striking in this series.

RESECTION RATE

TABLE IV. BGH AND RPMI. CARCINOMA OF THE ESOPHAGUS SERIES FROM 1947 TO 1953

NUMBER OF PATIENTS EXPLORED	NUMBER OF PATIENTS RESECTED
72 (RPMI)	36 (RPMI)
43 (BGH)	28 (BGH)
Combined resectability = 55.6 per cent.	

In both institutions a total of 64 patients were resected for this disease. One hundred and fifteen patients were explored. The combined resectability rate is 55.6 per cent. The figures for each institution are detailed above. No effort was made in compiling the figures to collect data bearing on operability rates, since the material available for inclusion in this study is already in one sense selected. Terminal cases never completely diagnosed, those seen in these institutions but treated elsewhere, and so forth, if included, would weaken the figure obtained and result in a distorted, meaningless operability rate. This figure is in reality, for the very reasons outlined above, often untrustworthy in most series published. The resectability rate, however, is more real and tangible. Table IV indicates that 55 per cent of the patients operated upon were resected. The obstacles to resection were usually unmanageable involvement of the respiratory tract (trachea, bronchi), extensive involvement of celiac nodes and liver, deterioration of the patient at surgery, or extensive rigid attachment of the tumor to aorta or vertebral bodies.

In dictating reports and analyzing statistics insufficient attention has been paid in the past to classifying an operation as one for *cure* or for *palliation*. This decision should be made at the conclusion of the operation when the surgeon responsible is best able to so designate the procedure. When the disease has not been grossly completely eradicated it is obvious that the operation was performed for palliation and the most optimistic operator should not expect a five-year survival. Nor should this case be listed in the figures which state the percentage of 5-year survivals following esophagectomy for cure as they tend to obscure the real outlook of the patient in whom we earnestly feel all visible disease has been removed. It is this last figure which is so important to know and so difficult to find clearly stated in the available figures. Unfortunately our own data are also singularly lacking in this useful information.

Resections for carcinoma of the esophagus are carried out in both these clinics by the method originally described by Lewis (England) and subsequently introduced in this country by one of the authors (J. E. M.) in 1946. This embodies two incisions, one abdominal and the other right thoracic. Its merits and disadvantages are not properly a part of this report. When the lesion was felt to lie at the cardia with esophageal extension a left transthoracic or

left thoracoabdominal incision was used. The mortality rates speak for themselves. A heroic attempt to resect extensive middle third lesions in the RPMI series led to more fatalities with no increase in survivals but served, as experience usually does, not only to clarify our judgment in regard to what type of lesion in this location is properly resectable, but also, and just as importantly, to warn us against undertaking resections under circumstances which prevented a satisfactory result in the interests of either cure or palliation.

RESECTION MORTALITY

TABLE V

LEVEL	RESECTED CASES	OP. MORTALITY
BGH		
Cervical	4	0
Middle one-third	8	0
Lower one-third	3	1
Cardia with esoph. extension	8	1
Total	28	5
17.8 per cent total operative mortality		
RPMI		
Cervical	1	0
Upper one-third	1	1
Middle one-third	20	6
Lower one-third	6	1
Cardia with esoph. extension	8	2
Total	36	10
28 per cent total operative mortality		

The tables for each of the two reporting hospitals are listed separately for better study. The survivals are arranged according to average in months. Both series indicate a strong benefit to be derived from resection when the lesions are middle or lower third in location. These figures have not been corrected by assigning the operative deaths a figure of 0 or ½ month survival as the case may be since this traditionally has not been done in the surgical literature. Were it to be done the true value of palliative surgery could more easily be determined in regard to duration of life. The condition of that life, its inconveniences and sufferings must be weighed in the balance. It is our own belief that after the initial impact of the surgery has passed the survivors live more comfortably than their unoperated fellows.

An examination of the living patients reveals only five surviving over five years out of a total of 64 resections. The fifth case, *G* in the BGH series, lived over five years but by January, 1955, had succumbed to the ravages of the disease. This then represents a five-year survival rate of 8 per cent for resected carcinoma of this organ, a depressing figure indeed.

In the RPMI table, 4 cases are listed as plastic inserts. In these cases the esophagus was resected and a Berman plastic tube replacement inserted. All patients died within one year of surgery of the effects of either massive local recurrence or the erosion of the tube.

SURVIVALS

TABLE VI. CARCINOMA OF THE ESOPHAGUS SERIES FROM 1947 TO 1953

BGH

SURVIVAL FROM DIAGNOSIS TO DEATH ACCORDING TO MANAGEMENT (AVERAGE IN MONTHS)

LEVEL	RESECTED*	PALLIATIVE TREATMENT‡	NO TREATMENT
Cervical	10.8	8.3	--
Upper one-third	6.3	5.8	--
Middle one-third†	20.8	7.2	1.0
Lower one-third	28.5	4.0	4.2
Cardia with esoph. exten.	9.7	6.0	6.5

*Cases still living and length of survival—(6 cases):

A, Cervical; 1 case; 11 months.
B, Upper one-third; 1 case; 1 year, 10 months.
C, Middle one-third; 1 case; 2 years, 3 months.
D and *E*, Lower one-third; 2 cases; 6 years, 5 months; 14 months (living with disease).
F, Cardia and Esoph.; 1 case; 1 year, 8 months (living with disease).
†One case (middle one-third) died of disease; 5 years, 5 months.
‡X-ray therapy, occas. gastrostomy.

RPMI

Cervical	7.0 (1 case)	0.0	4.0
Upper one-third	4.0	7.0	2.0
Middle one-third	12.5	5.5	6.5
Lower one-third	7.2	5.0	5.0
Cardia with esoph. exten.	20.2	5.0	5.5

Plastic tube insert.
Indiv. survivals (middle one-third)
6 mos.
9 mos.
1 mo. (breakdown of anastomosis)
6 mos. (breakdown of anastomosis)

Case still living and length of survival:

A, Middle one-third; 7 years.
B, Middle one-third; 9 months.
C, Cardia and Esoph.; 5 years.
D, Cardia and Esoph.; 5 years, 1 month.
E, Cardia and Esoph.; 2 years, 1 month.

SUMMARY

One hundred and thirty-eight cases of carcinoma of the esophagus and cardia of the stomach were treated by the surgical services of the Buffalo General Hospital and the Roswell Park Institute for Malignant Disease between 1947-1953.

115 patients were operated.
64 lesions were resected (55.6 per cent).
15 patients died before leaving hospital (23+ per cent).
5 patients lived over five years (approximately 8 per cent).

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INTUSSUSCEPTION: A HAZARD OF INTESTINAL INTUBATION

DWIGHT C. MCGOON, M.D.*

SOME authorities recommend preoperative intestinal intubation in preparation for certain types of abdominal surgery, especially when colonic resection is planned. This offers two advantages: It improves exposure during operation by facilitating the packing away of the small intestine, and its postoperative use averts intestinal distention.

While recently seeking to benefit from the advantages of this technique, a complication following right colonic resection was encountered which marred an otherwise uneventful postoperative course, and which is attributable directly to the intestinal intubation. This complication consisted of twice occurring intestinal intussusception, the latter instance developing some three weeks following removal of the Cantor tube. The unique pathogenesis of the intussusception seems apparent and demonstrable.

The complications of intestinal intubation which occasionally occur have been the subject of several studies.[1, 3, 4] However, the event which warrants this report has apparently been previously documented only twice,[2, 5] and in each instance a failure to appreciate the complication was believed to be responsible for the resulting fatality. An awareness of the possible occurrence of intussusception in association with intestinal intubation, although a rare complication, is therefore essential.

In the three known instances in which intussusception occurred as a result of intubation, an air-filled bag was utilized in one, and a mercury-filled bag in each of the other two. Paradoxically, it was the occurrence of this complication following the use of an air-filled bag which was one of the factors which led Harris[2] to experiment with the use of mercury.

PATHOGENESIS OF THE INTUSSUSCEPTION

Peristaltic waves act upon the bag at the end of an indwelling tube exactly as though it were a food bolus and force it distally within the intestinal lumen. However, the long tube trailing behind offers resistance to the forward movement of the bag, especially if the tube is anchored externally to the face. Since each action has an equal and opposite reaction, and since the bag in the intestine resists distal propulsion, the intestine itself is therefore drawn proximally over the semifixed bag and tube. Repeated peristaltic activity may thus draw the entire length of the intestine proximally about the bag until it is telescoped over

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a length of tube many times shorter than the length of the involved intestine. This telescoping of the intestine causes the formation of multiple "pleats," or plications, in the intestinal wall, as illustrated in Fig. 1.

This phenomenon surely occurs each time such a tube finds its way into the lumen of normal small intestine. Peristaltic activity in the telescoped or "pleated" area continues, and thus the plications are constantly altering their relations. There should be no more tendency for the adjacent peritoneal surfaces of each in-folded pleat to adhere than for normal adjacent loops of intestine. Consequently, upon withdrawal of the tube, plications disappear and the intestine returns to a normal status.

When, however, intraperitoneal conditions develop which are known to be conducive to adhesion formation, such as those following laparotomy or peritonitis, the adjacent peritoneal surfaces of each plication may adhere. The sticky fibrinous material exuded from inflamed peritoneal surfaces acts to "glue" and fix the plications, a tendency which is further fostered by the frequently associated ileus. If sufficient time be granted for the adhesive fibrinous exudate to organize, the plications then become more or less permanent. This condition is illustrated in Figs. 3 and 4.

Such a fixed plication resembles to some extent an intestinal polyp, with its luminal projection and its attachment to the intestinal wall. This fixed plication may thus act in the same well-known manner as a polyp to produce and lead an intussusception. This is illustrated diagrammatically in Fig. 2. This also accounts for the development of the intussusception even after withdrawal of the intestinal tube.

REPORT OF CASE

W. S., 49-year-old Negro man (Johns Hopkins Hospital No. 582122).—This muscular laborer had been entirely well until five months prior to admission, when right lower quadrant abdominal discomfort began, associated with anorexia and gradual weight loss.

Examination showed slight tenderness in the right lower quadrant, with a ballotable mass in the mid-right abdomen. A barium enema revealed a filling defect in the lower portion of the ascending colon.

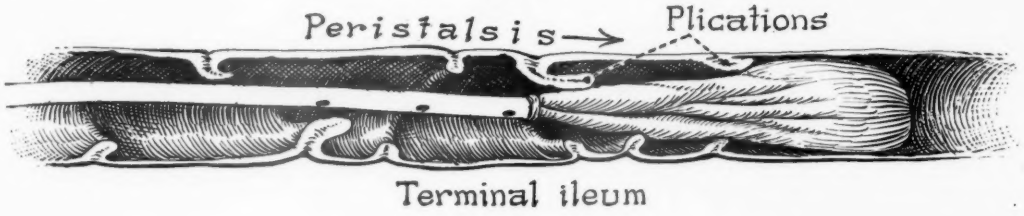
On Feb. 27, 1954, the patient was admitted to the hospital. Sulfasuccidine was begun four days preoperatively. Neomycin was begun thirty-six hours before operation, and at the same time a single lumen intestinal tube with a mercury-containing bag (Cantor tube) was passed into the stomach.

Right colectomy, with an end-to-end ileotransversostomy, was uneventfully performed in two hours and five minutes through a transverse incision. No evidence of liver or node metastases was found, and the malignant ascending colon lesion had not invaded surrounding structures locally. The Cantor tube was noted in the terminal ileum during the surgery.

Suction was applied to the Cantor tube postoperatively. Bowel sounds were audible on the third postoperative day, and suction was discontinued the following day. On that day peristalsis became vigorous, and abdominal "growling" was audible even at a distance. Vomiting occurred the following day, and suction was resumed. Abdominal cramping persisted in spite of decompression by the tube, and no flatus or feces were passed. Because this rather unusual development was suspected to be related in some way to the presence of the Cantor tube, it was removed on the sixth postoperative day. No relief from the cramping abdominal pains occurred, however, and vomiting continued. Intravenous feedings kept the serum electrolytes in normal range.

On the ninth postoperative day, exploratory laparotomy was performed, and a typical ileo-ileal intussusception was found which was so edematous and partially gangrenous that resection and end-to-end anatomosis were required. Numerous plications, fixed by fibrinous adhesions, were noted along the bowel wall, and were released by gentle manipulation insofar as possible.

Fig. 1.



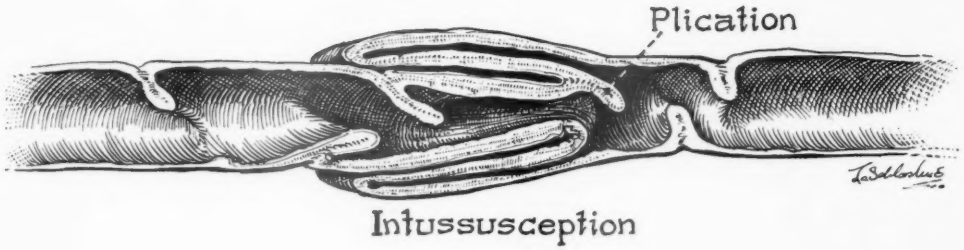


Fig. 2.

Fig. 1.—Intestinal wall plications which form as a result of peristaltic activity in the presence of the tube and its bag.

Fig. 2.—The manner in which a fixed plication, even after extubation, will act in the same well-known manner as a polyp to produce and lead an intussusception.

Fig. 3.—Photomicrograph of an actual fixed plication of a portion of the intestine removed from the patient reported in this paper (×6, reduced 2/7).

The early course following this procedure showed intermittent recurrence of the colicky abdominal pain, with intermittent abdominal distention and vomiting. Gradually these subsided, however, and by ten days following relief of the intussusception, the patient was ambulatory, passing feces and flatus per rectum, and was not distended. He was discharged twenty-two days following the right colon resection, and twelve days following resection of the intussusception.

The patient spent only four days at home, however, during which time he ate little, experienced intermittent colicky supraumbilical pains, and had scant watery bowel movements. On the fourth day vomiting recurred, the patient returned to the hospital, and was readmitted.

Examination at this time showed the patient to be in no acute distress, with normal vital signs. The abdominal incisions were indurated, but no abdominal masses were felt. The abdomen was only slightly distended and the left abdomen was tympanitic.

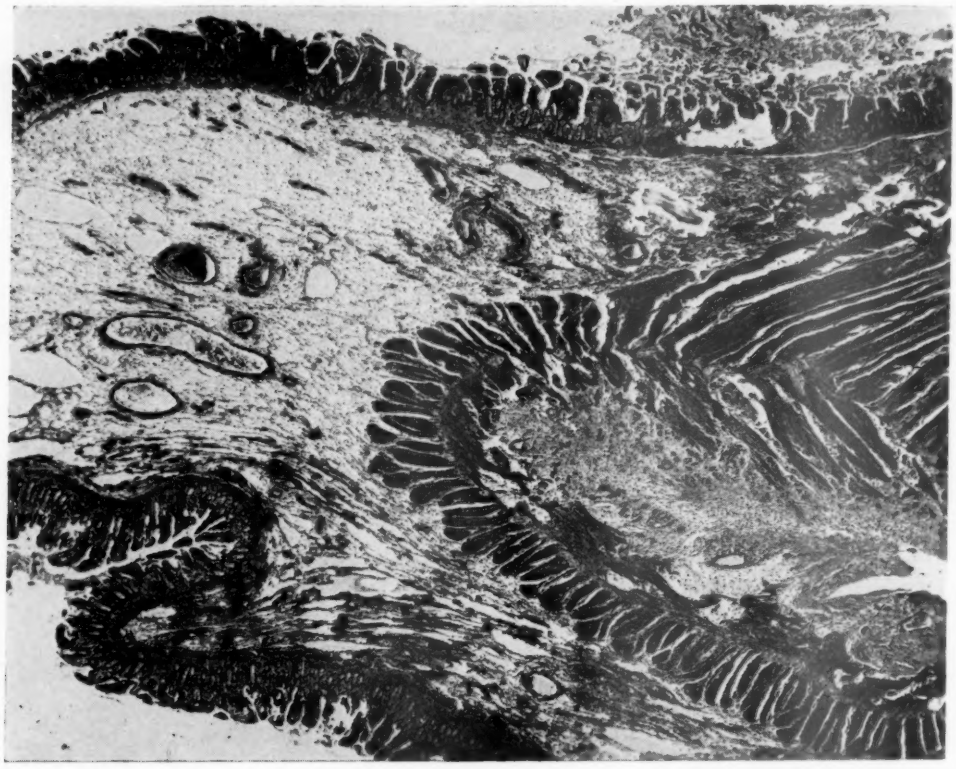


Fig. 4.—An enlargement of the central portion of the photomicrograph in Fig. 3, showing organization of the fibrinous adhesive material between the peritoneal surfaces of the plication, causing it to be permanent, or fixed (×15).

Two days after readmission bowel movements stopped, and the abdomen became distended. Three days of intermittent gastric suction were then employed, during which time some flatus was passed. Repeated abdominal films showed no clear indication of intestinal obstruction. Serum electrolytes were never significantly altered. No essential clinical improvement was noted, however, so the third operation was performed thirty days following the original right colon resection, and twenty-one days following resection of the intussusception.

At this third laparotomy, another intussusception was encountered at about the level of the terminal jejunum, which by persistent gentle manipulation was successfully reduced proximally until finally released. No resection was required. Further plications in the intestine were noted, but had become fixed by organized adhesions by this time and could only partially be released.

The patient showed progressive improvement thereafter, though occasional and variable colicky abdominal pain were experienced for several days. Eighteen days following the final surgery he was discharged, and remained well and working for six months, at which time he was lost to follow-up.

CONCLUSIONS

Because of the fact that intussusception is such an exceedingly rare complication of intestinal intubation, it should offer relatively little contraindication to the use of this helpful therapeutic device. However, the possible occurrence of such a complication does introduce a note of opposition to the practice of using intestinal intubation routinely as an adjunct to certain abdominal surgical procedures. Furthermore, the possibility of this complication must be borne in mind, so that its occurrence may be ascertained early, and its confirmation and treatment by laparotomy be timely. In addition, once the plications of the intestinal wall have become permanently fixed, they may cause the development of intussusception even after the intestinal tube has been withdrawn.

SUMMARY

1. Intestinal intussusception may occur rarely as the result of intestinal intubation, the instance included in this paper representing the third such case recorded.

2. It is believed that this occurs secondary to the presence of intestinal wall plications, which form as a result of peristaltic activity in the presence of the tube and its bag. The plications then act to produce intussusception as would a polyp.

3. Peritoneal inflammation from whatever cause may result in persistence of the plications even after extubation, and thus the threat of intussusception also lingers.

4. Though a rare complication, the possibility of its occurrence must be considered in the employment of intestinal intubation.

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THE EFFECT OF GANGLION-BLOCKING AGENTS ON SURVIVAL OF RATS SUBJECTED TO ACUTE THERMAL INJURY

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THE survival-promoting quality of adequate fluid and electrolyte replacement in burned man and experimentally burned animals has recently received thorough verification.[5, 15-17] On the other hand, a recent renewed attempt to improve survival rates by means of a pharmacologic agent[11] has not been confirmed.[14] The lowered mortality in humans suffering from extensive burns, as indicated by a recent study,[18] can be attributed in large part to the rapidity and adequacy with which fluid therapy has followed the initial burn.

The part played by the nervous system in producing the picture of shock, although accepted as important, is far from having been elucidated. Nevertheless, a partial insight into the mechanism relating the nervous system to certain hemodynamic phenomena has been recently provided by evidence indicating that adequate block of efferent autonomic impulses may, if properly controlled, reduce the blood loss at the operation site and thus reduce the frequency of shock associated with traumatic procedures.[6] This phenomenon, known as controlled hypotension, in contrast to hypotension produced by experimental hemorrhage, can be tolerated for considerably longer periods without damage to vital organs since it is not accompanied by compensatory vasoconstriction.[20] This ability of ganglion-blocking agents to reduce blood loss during surgical procedures prompted this attempt to answer the question whether such substances were capable of reducing fluid loss and prolonging survival in animals subjected to an extensive experimental burn. It was also attempted to determine whether animals thus treated were still able to benefit from the survival-promoting qualities of intravenous fluid therapy administered after a considerable postburn delay.

METHODS

Male albino rats, of a local pure strain, ranging in weight from 150 to 265 Gm. were used. The data represent experiments performed on some 450 rats. The animals were housed in wire cages at a room temperature of 23 ± 2° C. and fed a balanced diet in the form of dried pellets and water ad libitum. Burns were produced according to the method described by McCarthy[13] with the following slight modification: anesthesia was induced by placing the animals under a 3-L. bell-jar through which an oxygen-ether mixture was allowed to pass for exactly four minutes. This time was found adequate for producing a type of anesthesia whereby the rats would be awake within one minute postburn. The burn was

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produced by immersing the backs of the anesthetized rats into water at 90 ± 2° C. for exactly thirty-five seconds. Following immersion the excess water was removed by rolling the animals upon a cloth towel and on completion the substances to be tested injected into the lateral tail vein in the following quantities:

1. Azamethonium (Pendiomid*): 2 mg. in 0.2 c.c. of 0.9 per cent NaCl.
2. Hexamethonium bromide (Vegolysen†): 1 and 2 mg. in 0.2 c.c. of 0.9 per cent NaCl per mg.
3. Controls received an equal quantity of 0.9 per cent NaCl.

Time of death was recorded to the nearest five minutes. Pretreated animals received 2 mg. azamethonium in a similar manner one-half hour prior to burning. At death the burned skin was excised, the burned area copied onto cellophane, and the area determined by planimetry. The excised skin was cut into two sections and the natural curvature of the skin straightened by an additional incision at right angles to the dividing cut. This procedure permitted adequate flattening of the skin by hand under the cellophane without additional mechanical stretching. Total body surface was calculated from the formula: $S = KW^{0.6}$, where K = 12.54 and W = weight of animal.

Preparation of Animals for Intravenous Infusion.—In order not to add the trauma of an operation to the standard burn procedure rats were anesthetized 24 to 72 hours prior to burning and a P20 polyethylene catheter filled with 0.1 per cent heparin introduced into the priorly exposed right jugular vein. Exposure was obtained by a small (ca. 0.5 cm.) incision on the ventral aspect of the neck immediately above the rib cage. Once introduced into the vein the catheter was passed down into the direction of the right heart chamber until it rested just above or below the opening into the right atrium. The catheter was secured in the vein with silk suture ties and the distal segment of the vein ligated. The free end of the catheter, which had been previously knotted in order to prevent leakage of its contents, was next passed under the skin around to the back of the neck by sliding it through a wide hypodermic needle introduced by a stab incision in back of the occiput. The catheter was thus resurfaced in back of the head and at the point of emergence anchored to the skin. The protruding segment (ca. 2-3 cm. long) was pushed under the skin of the back with a pair of forceps, and the ventral incision completely closed. Following the operation the rats received 20,000 units of penicillin intramuscularly and were placed into individual wire cages with food and water being allowed ad libitum. In the described location behind the neck the catheter is beyond the animal's reach and patency and thus accessibility to intravenous infusion was found as late as one week following insertion. The burning procedure for these animals was identical to the one described above except that the small segment of catheter reburied at the conclusion of the operation was first withdrawn from its subcutaneous position in order to prevent damage by the hot water. Animals operated upon received 2 mg. azamethonium (Pendiomid) into a lateral vein of the tail immediately postburn and the polyethylene segment was joined to a P90 polyethylene catheter which was, in turn, attached to a hypodermic needle and syringe through which fluid was administered. Fluid therapy consisted of 1.4 per cent NaCl amounting to 5 per cent body weight and delivered as a constant infusion from the eighth to the twelfth hour postburn. At the end of this period surviving animals were returned to their cages and sacrificed after forty-eight hours in order to determine the area burned. Location and patency of the jugular catheter were checked at autopsy in every case.

Fisher's t-test[8] for the significance of differences of mean survival times was employed to determine the effect of therapy.

RESULTS

In order to ascertain that differences in mean survival time were due to no other factor(s) than treatment, the 2 groups comprising the upper and

*N, N, N′, N′, –3 pentamethyl-N, N-diethyl-3-aza-pentane-1, 5-diammonium dibromide was generously supplied by Dr. H. J. Bein of Ciba Ltd., Basel, Switzerland.

†Vegolysen made by May & Baker Ltd., Degenham, England.

lower extremes in weight and burned surface were compared. In Fig. 1 the two extreme weight groups, that is, 150 to 190 and 220 to 265 grams, were compared and the difference in mean survival time found not to be significant, p being greater than 0.05. In Fig. 2 the two extremes in burned surfaces, that is, 24 ± 2 per cent and 29 ± 2 per cent, showed no significant difference between means, t equalling 0.378 and p being greater than 0.70. Based on these findings all subsequent data included animals weighing 150 to 265 grams and having received a body burn of 27 ± 4 per cent of their body surface.

The influence of azamethonium (Pendiomid), given either one-half hour prior to or immediately following the burn, on mean survival time is illustrated in Fig. 3. In both instances the difference proved to be significant, t equalling 4.366 and p being less than 0.001 in the pretreated group while t equalled 3.265 and p was less than 0.01 in the case of after-treatment.

The amount of azamethonium employed was in the LD_{50} range for the mouse, a range which may be assumed to apply to the rat as well.[3] This dosage was chosen in order to make evident any difference which might be afforded by treatment. Since both the heuristic and practical values of after-treatment exceed that of pretreatment, the effects of hexamethonium were investigated only when this substance was given in the postburn period. The results are presented in Fig. 4. Thus if hexamethonium is given immediately postburn in a quantity of 1 mg. intravenously mean survival time is significantly prolonged, t being 3.125 and p less than 0.01. Increasing the amount of hexamethonium given to 2 mg. results in a disappearance of the beneficial effect and treated animals die as rapidly as controls, t for the difference of the means being 0.04.

Fig. 5 represents the data obtained on pre-operated rats receiving 2 mg. azamethonium immediately postburn and a constant infusion of 1.4 per cent NaCl amounting to 5 per cent of body weight between the eighth and twelfth hour following burning. Treated animals showed no significant prolongation in mean survival time over controls, t being 0.222. On the other hand operated controls showed a significantly longer mean survival than unoperated controls, t being 2.515 and p less than 0.02. In addition, approximately one-half of the operated animals, whether treated or not, still surviving at the time when the saline solution infusion was started, survived beyond the twenty-four-hour period. None of the 450 animals employed in this experiment, including those whose burned surface did not comply with the required standard, survived beyond 16 hours following burning if no fluid was replaced.

Table I summarizes survival at different periods postburn in those groups in which a significant prolongation of mean survival time over corresponding controls was obtained. Although the number of animals in the hexamethonium-treated and operated controls group is too small to allow for definite conclusions, a definite trend by these animals to survive in greater numbers following an extensive burn can be seen. These differences were shown to be statistically significant (see above). After eight hours approximately one-half of the aforementioned two groups were still alive while among controls only some 3 per cent were still surviving.

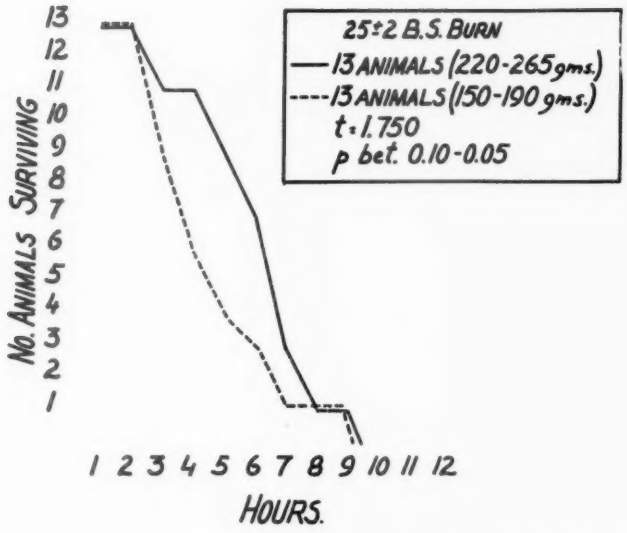

Fig. 1.—Curves comparing survival in two extreme weight groups. Due to small number of animals compared, the number rather than the per cent surviving is plotted on the ordinate.

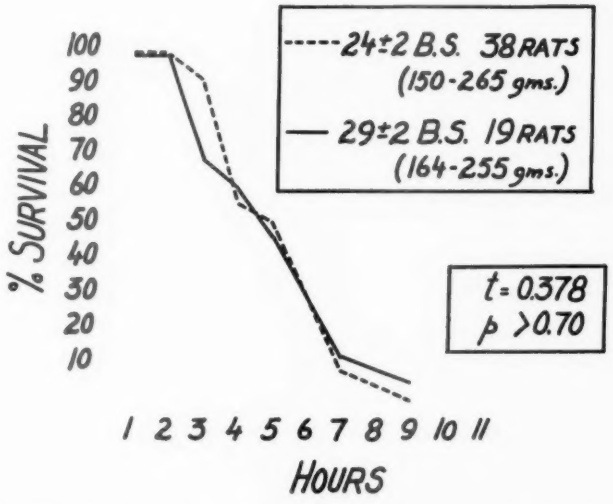

Fig. 2.—Curves comparing survival in two extremes in burned surface area.

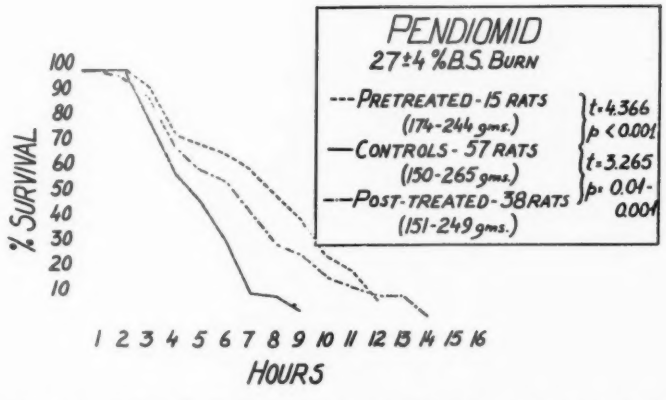

Fig. 3.—Survival curves for rats receiving a standard burn, one group being pretreated and another immediately after burning with 2 mg. azamethonium (Pendiomid) intravenously. Pretreatment one-half hour prior to burning.

Table II presents a general summary of the experiments performed and the data obtained. Statistically significant differences in mean survival time were found when comparison was made in the following groups: (1), Pre-treated with 2 mg. azamethonium and corresponding controls; (2), Post-treated with 2 mg. azamethonium and corresponding controls; (3), Post-treated with 1 mg. hexamethonium and corresponding controls; (4), Animals operated twenty-four to seventy-two hours prior to burning and unoperated controls.

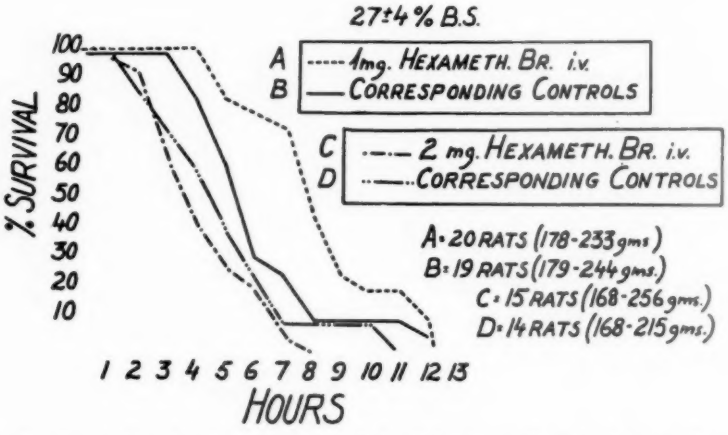
27±4% B.S.
A ----- 1mg. HEXAMETH. BR. i.v.
B —— CORRESPONDING CONTROLS
C -·-·- 2 mg. HEXAMETH. BR. i.v.
D ·····—···· CORRESPONDING CONTROLS
A·20 RATS (178-233 gms)
B·19 RATS (179-244 gms.)
C·15 RATS (168-256 gms.)
D·14 RATS (168-215 gms.)
% SURVIVAL
100 90 80 70 60 50 40 30 20 10
1 2 3 4 5 6 7 8 9 10 11 12 13
HOURS

Fig. 4.—Survival curves for burned rats treated with 1 or 2 mg. hexamethonium bromide intravenously immediately postburn.

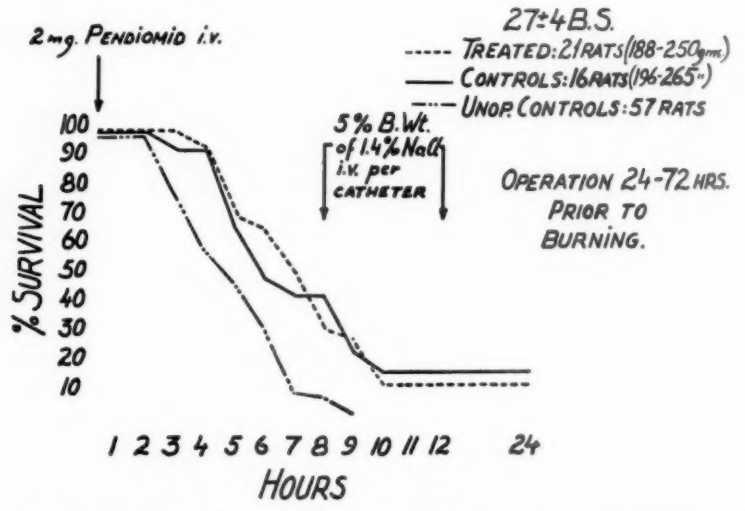
2 mg. PENDIOMID i.v.
27±4 B.S.
----- TREATED: 21 RATS (188-250 gms.)
—— CONTROLS: 16 RATS (196-265 gms.)
---- UNOP. CONTROLS: 57 RATS
5% B.Wt. of 1.4% NaCl i.v. per CATHETER
OPERATION 24-72 HRS. PRIOR TO BURNING.
% SURVIVAL
100 90 80 70 60 50 40 30 20 10
1 2 3 4 5 6 7 8 9 10 11 12 24
HOURS

Fig. 5.—Survival curves of preoperated rats receiving 2 mg. azamethonium (Pendiomid) intravenously immediately postburn and an infusion of 1.4 per cent NaCl (5 per cent body weight) from the eighth to the twelfth hour postburn.

DISCUSSION

Controlled hypotension which may be produced by the use of ganglion-blocking agents has found application in surgery partially by virtue of its ability to reduce both bleeding during operations and the frequency of post-

operative complications usually associated with great losses of fluid.[4, 6] Such fluid loss plays a major part in producing the classical picture of shock in the experimental animal and its significance in promoting survival, when properly replaced, has recently been well documented by McCarthy and coworkers[15, 16] in the rat and Millican and associates[17] in the mouse subjected to a standardized burn. Aside from other changes contributing to shock and which it may incite, fluid loss is always accompanied by an increase in peripheral vasoconstrictor tone thus allowing the organism a relatively efficient means of redistributing the residual blood volume. Once this situation has arisen, removal of the tone, be it by anatomic or chemical means, can only prove disastrous since the resulting peripheral pooling will deprive vital organs of a critical supply of blood. The sequence of these events and their importance for survival is demonstrated by studies in which reduction in vasoconstrictor tone has been produced either before or after a standard traumatic procedure.

TABLE I. SURVIVAL AT DIFFERENT PERIODS POSTBURN*

TREATMENT	PER CENT AREA BURNED	NO. RATS	ALIVE AT 2 HR.	4 HR.	6 HR.	8 HR.	10 HR.	12 HR.
Controls	27 ± 4	76	75	49	24	2	2	0
Pendiomid	27 ± 4	38	36	26	21	11	7	4
Hexamethonium	27 ± 4	20	20	20	16	9	4	2
Operated controls	27 ± 4	16	16	15	8	7	3	3

*Indicates the number of surviving animals in various groups at different periods following burning. Included are only those groups which show a statistically significant prolongation of mean survival time over controls.

TABLE II. SUMMARY OF THE EXPERIMENTS AND DATA OBTAINED

GROUPS COMPARED	NO. RATS	PER CENT AREA BURNED	WEIGHT (GM.)	MEAN* SURVIVAL TIME ± S. E.	t	p
150-190 gm.	13	25 ± 2	—	265 ± 34	1.750	0.10-0.05
220-265 gm.	13	25 ± 2	—	349 ± 33		
24 ± 2 B.S.	38	—	150-265	280 ± 23	0.378	>0.70
29 ± 2 B.S.	19	—	164-255	294 ± 24		
Pretreated with 2 mg. Pendiomid	15	27 ± 4	172-244	469 ± 54	4.366	<0.001
Controls	57	27 ± 4	150-265	290 ± 16		
Post-treated with 2 mg. Pendiomid	38	27 ± 4	151-249	401 ± 34	3.265	0.01-0.001
Post-treated with hexamethonium (1 mg.)	20	27 ± 4	178-233	481 ± 33	3.125	0.01-0.001
Controls	19	27 ± 4	179-249	356 ± 29		
Post-treated with hexamethonium (2 mg.)	15	27 ± 4	168-256	276 ± 37	0.04	—
Controls	20	27 ± 4	168-227	278 ± 31		
Operated + Pendiomid	21	27 ± 4	188-250	381 ± 22	0.222	—
Operated controls	16	27 ± 4	196-265	373 ± 29	2.515	0.02-0.01
Unoperated controls	57	27 ± 4	150-265	290 ± 16		

*Time in minutes.

Freeman[9] demonstrated originally that totally sympathectomized dogs withstood hemorrhagic hypotension better than corresponding unoperated controls although they reacted with greater changes in blood pressure to smaller losses of blood. Similar results have been obtained more recently by Baez, Zweifach, and Shorr[2] who produced a form of peripheral sympathectomy by pretreating their animals with Dibenamine and its congeners.[22] Glasser and Page[10] subjected dogs treated with tetraethylammonium to a standard hemorrhage and found improved survival in both the good and bad prognosis groups. Significant is the fact that in all studies where chemical blockade was attempted in the presence of hemorrhagic hypotension, improved survival was found only when blocking had been carried out prior to bleeding. Glasser and Page treated dogs also after hemorrhage had taken place, but analysis of their results is complicated by the fact that these animals were allowed to redraw lost blood from the reservoir in order to maintain a prescribed blood pressure level which had been excessively lowered by treatment with the ganglion-blocking agent.

Hypotension alone, in the absence of fluid loss, is not as deleterious as hypotension produced by hemorrhage. This is due to the prolonged compensatory vasoconstriction which invariably follows the latter. Aynlan and associates[1] found that dogs subjected to chemical hypotension with Arfonad, a ganglion-blocking agent, exhibited a lower mortality than dogs in which hypotension had been produced by hemorrhage. Although the hemodynamic readjustments to fluid replacement in an animal subjected to an extensive burn or hemorrhage are quantitatively similar, these two shock-producing methods differ in one important aspect, namely, the rate of initial fluid loss. In laboratory hemorrhage this rate can be well controlled by the individual experimenter and rapidity of bleeding is very much a matter of choice. In a burn, however, certain parameters (blood pressure, depth of burn) control the rate of loss and these combine in such manner that maximum loss is achieved much later than after hemorrhage.[5, 19] The difference in this rate of fluid loss is important because it allows for an explanation of the beneficial effect afforded by ganglion-blocking agents when administered immediately following the burn. The resulting hypotension is achieved by removing excessive vasoconstrictor tone arising in the early stages postburn as a result of (1) an increased discharge of nociceptive stimuli from the burned area and (2) fluid loss into the affected region. Removal of excessive tone occurs at a moment when adjustment to such a change is still possible, that is, when the animal is still in possession of a near normal effective extracellular fluid volume. Similar conclusions have already been proposed by Phemister and Laestar[21] who found that spinal anesthesia protected dogs against shock developing subsequent to limb trauma. In regard to the added pressor effect of nociceptive stimuli, Wang and Overman[24] found that dogs submitted to hemorrhage alone survived the period of shock better than dogs in which artificial stimulation of afferent nerves had been added to hemorrhage or muscle trauma as the shock-producing method.

As blood pressures were not recorded in our experiments it is not possible to substantiate directly the above statements. Repeated measurement of

plasma and red-cell volume with and without treatment may provide the full answer; however, on the basis of the known actions of ganglion-blocking agents in man and the experimental animal the explanation appears plausible.[4, 20] Chemical hypotension probably reduces the rate at which fluid is lost into the burned area by reducing blood pressure and prolongs mean survival time by delaying the point beyond which additional loss is no longer compatible with life.

The finding that animals previously operated survive longer than unoperated controls, whether the former have been treated or not, makes such a simplified explanation difficult to accept. Nevertheless, in the absence of evidence to the contrary, it is very likely that we are faced with two different phenomena and the survival value of conditioning to trauma is probably greater than that of hypotension produced with the intention of reducing fluid loss. Conditioning to trauma has recently found renewed support in rats subjected to other forms of experimental injury,[23] but the mechanism responsible has not received satisfactory explanation. It has been suggested that the liver might play a major part in giving rise to this phenomenon.[7, 23] Our experiments provide no insight into the pathways by which this phenomenon is mediated but it is apparent that if hypotension does occur in the operated and treated animals then it has no great positive influence on survival when compared to corresponding controls. Thus ganglion-blocking agents, when used in the immediate postburn period, have, in all probability, primarily a palliative effect and little influence on survival beyond a certain point if fluid therapy is completely disregarded.

Another possible explanation for the beneficial effect of substances exerting lytic or blocking effects on the autonomic nervous system is provided by the recent finding by Henry[12] that hyperkalemia due to excessive epinephrine release following a burn may be prevented by treating animals with piperoxan hydrochloride (Benodaine hydrochloride).

Interesting to note is the fact that the intravenous infusion of slightly hypertonic saline solution (1.4 per cent), administered in amounts of 5 per cent of body weight eight hours postburn was able to promote survival beyond the twenty-four-hour period. As mentioned earlier none of the animals who did not receive replacement therapy survived longer than sixteen hours. According to McCarthy and co-workers[15, 16] the quantities of saline solution used are inadequate when ten-day survival is used as a criterion. However, it is clear that even these supposedly inadequate quantities allowed half of the animals receiving such therapy to survive beyond the period which lack of fluid replacement would have allowed. Whether this is also due to the conditioning phenomenon is impossible to state at the moment.

CONCLUSIONS

1. Treatment of rats subjected to a standard hot water burn at 90 ± 2° C. for thirty-five seconds with ganglion-blocking agents (hexamethonium or azamethonium, a substituted pentamethonium compound) has a positive, statistically significant effect in prolonging mean survival time.

2. In the absence of other direct evidence it is suggested that such treatment in the immediate postburn period probably results in hypotension which in turn is responsible for a reduction in the rate of fluid lost into the burned area.

3. Body trauma in the form of an operation performed recently prior to burning increases the animal's resistance to burning to the extent that it survives longer than the unoperated control. The use of blocking agents in conditioned animals affords no additional protection. This has been found to be the case in animals operated upon twenty-four to seventy-two hours prior to burning.

4. Animals that show evidence of conditioning and have received an extensive body burn are still able to benefit from the survival-promoting qualities of intravenous hypertonic (1.4 per cent) saline when the latter is given as late as eight hours postburn.

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THE EFFECT OF INDUCED ARTERIOSCLEROSIS ON FRESH AND LYOPHILIZED AORTIC HOMOGRAFTS IN THE RABBIT

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ALTHOUGH the concept of utilizing aortic homografts for the replacement of diseased or traumatized aortic segments is based upon experiments performed over forty years ago,[2, 3] only recently have such procedures been applied to the human. Evidence is rapidly accumulating which indicates the satisfactory, immediate results of such procedures. Unfortunately, sufficient time has not elapsed to allow for an adequate appraisal of the long-term results. Since the vast majority of homografts have been utilized to restore the luminal continuity in aortas exhibiting such severe manifestations of arteriosclerosis as thrombosis or aneurysm, it appears germaine to inquire whether such grafts will ultimately develop this degenerative process. Aside from the report of DeBakey and associates,[7] who did not observe arteriosclerosis in aortic homografts in several patients one year following transplantation, no data concerning this significant problem has yet been presented. It would appear, in the light of recent concepts that arteriosclerosis may be an intermittent process, that a longer time interval would be required to evaluate whether human homografts develop arteriosclerosis.

Many investigations concerning the fate of aortic grafts in the experimental animal have been presented.[3, 4, 13-15, 19, 20, 22, 23, 26, 29] Degenerative changes characterized by a loss of the smooth muscle fibers of the media, replacement of the intima and adventitia of the graft by fibrous connective tissue derived from the host vessel, and calcification have been consistently described. This latter has been observed with great frequency in canine grafts preserved in formalin.[22] The influence of the pH of the fixative appears to play a significant role in this process, since variations in this factor resulted in a decreased incidence of calcification. Similar mineral deposits have been observed by Coleman and associates[4] in quick-frozen and nutrient-preserved grafts in dogs four years following transplantation. Although calcification not infrequently occurs in human arteriosclerosis, the degenerative changes referred to are more reminiscent of a nonspecific reaction to devitalized tissue, or the Mönckeberg type of arteriosclerosis, rather than that observed in the clinically significant atheromatous form of human arteriosclerosis characterized by intimal lipid deposits as well as fibrosis and occasional calcification.

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Although specific reference to arteriosclerosis is made in other studies, the significance of the observations described is often difficult to interpret. One small intimal arteriosclerotic plaque was noted by Keefer and associates[15] in one dog two years following the placement of a thoracic autograft. Swan and associates[26] recorded the presence of intimal macrophages as well as calcification in the homografts of dogs after five months. Sauvage and Harkins[23] concluded from their studies in the pig that arteriosclerosis was no more prone to occur in autografts than in the host vessels, but that homografts may show a greater tendency for such change. The experiments of Gentsch and associates,[12] utilizing hypervolemic infusions of lipid emulsions in dogs, demonstrated the susceptibility of homografts to acute injury. Greater lipid deposits and calcification occurred in the grafts than in the host vessels.

Because of the paucity of information concerning the development of arteriosclerosis in aortic grafts and the uncertain relationship of the degenerative changes cited to this process, it appeared advantageous to investigate the fate of aortic grafts in rabbits with induced arteriosclerosis. This species has long been known to develop arteriosclerosis with relative rapidity and unerring constancy when fed cholesterol. Since controversy exists in regard to the relationship of experimental cholesterol arteriosclerosis to human arteriosclerosis, it was realized that the results of this study might not be completely analagous to the fate of aortic grafts in the human in this respect. Yet, it was also appreciated that the reproduction of a disease in the experimental animal in the past has offered for a better understanding of its human counterpart. In addition, it recently has been stated by Duff and his colleagues[18] that it is probable that the mechanisms concerned in the pathogenesis of experimental cholesterol arteriosclerosis of the rabbit and human arteriosclerosis are similar in kind if not degree.

MATERIAL AND METHODS

Albino rabbits of both sexes, weighing 3 to 5 kg., were utilized in this study. The animals were anesthetized with intravenous sodium pentobarbital. A low midline abdominal incision was made and the intestines retracted to the left. With the aid of a binocular, magnifying loupe, approximately 2.5 cm. of the terminal aorta was dissected free from the vena cava and surrounding connective tissue and transected between two small serrefine clamps. The cut ends were allowed to retract and either a lyophilized or fresh homograft approximately 2 cm. in length was transplanted, using 5-0 arterial silk. Preliminary studies in which segments of aorta were resected before transplantation were associated with almost 100 per cent mortality because of thrombosis. In order to avoid constriction at the sites of anastomosis, the lumen was quadrangulated and each quarter anastomosed, using a continuous over-and-over stitch. Moderate oozing from the suture line occurred when the clamps were removed, but this was readily controlled by light pressure with a gauze sponge maintained for several minutes. The administration of heparin also resulted in a reduction of mortality. All animals received a slow, intravenous infusion of heparin (1 mg./ml.) in saline solution after the induction of anesthesia until the completion of the procedure. Approximately 50 ml. of fluid was used in each animal. With this technique a total of 16 rabbits survived for sufficient periods to allow for evaluation of the effect of experimental cholesterol arteriosclerosis upon homografts.

All animals were fed Rockland rabbit ration pre- and postoperatively. Fourteen rabbits, 6 with lyophilized grafts and 8 with fresh grafts, received cholesterol in their ration

following operation, as depicted in Table I until the time of sacrifice. The cholesterol was administered by dissolving 5 gm. of cholesterol powder (USP Armour) in 200 ml. of ether per each 500 Gm. of ration. This was then poured over the food so that after evaporation of the ether the pellets were uniformly coated with cholesterol. Two additional animals with lyophilized grafts did not receive cholesterol in their ration.

TABLE I.—THE DURATION OF CHOLESTEROL FEEDING AND ITS EFFECT UPON HOMOGRAFTS IN THE RABBIT

METHOD OF PRESERVATION	DURATION OF GRAFT (DAYS)	DURATION OF CHOLESTEROL (DAYS)	SERUM CHOLESTEROL: CHOLES. ESTERS (MG. PER CENT)	CHANGES IN GRAFT
1. Freeze-dried	81	74	490:400	Arteriosclerosis
2.	82	75	880:700	Arteriosclerosis
3.	80	73	620:510	Arteriosclerosis
4.	82	75	810:670	Arteriosclerosis
5.	80	73	710:630	Arteriosclerosis
6.	27	26	*	Moderate arteriosclerosis
7.	80	None	180:90	No arteriosclerosis
8.	41	None	205:115	No arteriosclerosis
1. Fresh	218	110	690:380	Arteriosclerosis and aneurysm
2.	200	92	740:510	Severe arteriosclerosis
3.	104	103	880:660	Arteriosclerosis and aneurysm
4.	104	103	900:740	Arteriosclerosis
5.	104	103	860:620	Arteriosclerosis and slight ectasia
6.	112	107	*	Arteriosclerosis and occlusion
7.	112	107	*	Arteriosclerosis and occlusion
8.	45	42	*	Arteriosclerosis and ruptured aneurysm

*Animal died.

The fresh homografts employed were transplanted the same day they were removed aseptically from donor rabbits. Lyophilized grafts were prepared by a technique similar to that employed for the dog and humans in this laboratory and described elsewhere,[10] except that the period of lyophilization was reduced to eight hours.

Blood was obtained by venipuncture for the determination of total serum cholesterol and cholesterol esters according to the method of Liebermann-Burchardt prior to sacrificing the rabbits at the time intervals noted in Table I. The aortas were dissected free and opened longitudinally. Representative examples containing each type of graft were then stained en bloc with Sudan IV. All aortas were fixed for twenty-four hours in 10 per cent neutral formalin. Blocks were embedded in paraffin and sections taken to water in the usual manner and stained with hematoxylin and eosin; Verhoeff, Van Gieson elastic and connective tissue method; peracetic acid-Schiff procedure for the determination of unsaturated compounds[17]; thionin, 0.05 per cent for ½ hour at pH 4 with alcohol differentiation for the estimation of metachromasia; and Wilder's reticulum method. Frozen sections of wet formalin fixed tissue were cut at 10 μ and stained with oil red O for lipids; Schultz modification of the Liebermann-Burchardt reaction for cholesterol and cholesterol esters[17]; and sections were also placed in digitonin, stained with oil red O, and examined with polarized light for the estimation of free cholesterol according to the method of Windaus.[17]

RESULTS

Macroscopic Observations.—Firm, white, and yellowish-tan intimal plaques which appeared red when stained en bloc with Sudan IV were noted at necropsy in all grafts from rabbits fed cholesterol. Although such plaques were discrete and localized principally about the orifices of the branches of the aorta in the host vessel, they were confluent and of greater intensity within the

grafts (Fig. 1). Extension for several millimeters on to the host vessel adjacent to the lines of anastomosis was also present. In one rabbit receiving cholesterol for only 26 days this change was of less intensity. Although slight transverse luminal projections were noted at the lines of anastomosis, thrombosis was not encountered. Intimal plaques were not evident in the grafts or host vessels of the two animals with freeze-dried grafts which did not receive cholesterol.

The degree of arteriosclerotic change appeared greater in the fresh grafts than those prepared by freeze-drying. In addition, aneurysmal dilatation with thrombus formation was noted in 3 of the 8 animals with fresh grafts (Fig. 2). One of these had ruptured resulting in the death of the rabbit 45 days after transplantation. Slight ectasia of one fresh graft and stenosis with marked luminal narrowing were noted in two rabbits with this type of graft. On the other hand, aneurysm or stenosis was not observed in lyophilized grafts.

The adventitial surface of the grafts was only slightly thickened with apparently little host reaction at this site, since there was little difficulty encountered in the removal of the aortas at necropsy.

The total serum cholesterol and cholesterol esters were markedly elevated in all animals receiving the cholesterol feedings in which these determinations were performed.

Microscopic Observations.—Quantitative, as well as qualitative differences between the freeze-dried and fresh homografts of animals subjected to cholesterol feeding was evident. The intima of the fresh graft was formed by fibrous connective tissue of varying cellularity and thickness apparently derived from the sites of anastomosis which revealed a marked reparative process. Endothelial cells were not identified except in one instance. On the other hand, the luminal surface of grafts prepared by freeze-drying was comprised, for the most part, of compressed elastic tissue fibers of the media. Pannus of fibrous connective tissue extended for varying distances over the luminal surface of freeze-dried grafts, but in no instance did it completely cover the graft as was noted with the fresh homografts. However, this difference might be due to the fact that the fresh grafts were of longer duration. Increased ground substance was observed in the newly formed intima of both types of grafts at the lines of anastomosis, and particularly when such connective tissue change was dense and relatively acellular. The intimal pannus of the freeze-dried grafts and the intima of the fresh grafts were infiltrated with sudanophilic lipophages, as well as extracellular deposits of sudanophilic material (Fig. 3). More abundant accumulations were observed in the fresh homografts as was suspected from the gross appearance of the lesions at the time of necropsy. In the fresh grafts revealing occlusion the lumens contained plaques of loosely formed connective tissue containing numerous lipophages and extracellular lipid (Fig. 4). In those fresh homografts with aneurysmal dilatation the intimal fibrosis was severe with areas of increased ground substance, and fibrin thrombi containing lipophages were present projecting into the lumen of the vessel. The elastic fibers of the media of the freeze-dried grafts appeared, for

Fig. 1.

Fig. 2.

Fig. 1.—Aorta with lyophilized graft from rabbit with induced arteriosclerosis stained en bloc with Sudan IV. The luminal surface of the graft contains an arteriosclerotic plaque extending on to adjacent portions of the host vessel. Arteriosclerotic change is present at orifices of intercostals.

Fig. 2.—Aorta with fresh graft from rabbit with induced arteriosclerosis revealing aneurysmal dilatation and severe arteriosclerosis in the graft. Moderate arteriosclerosis is noted at the orifices of aortic branches.

the most part, well-preserved and continuous. Some compression toward the luminal surface of the grafts was present, as noted previously. The smooth muscle cells of the media were not evident, although reticulum fibers commonly associated with such cells were normal in appearance. Extracellular, as well as intracellular deposits of lipid were observed between, and on occasion, apparently coating the elastic tissue fibers (Figs. 5 and 6). There was

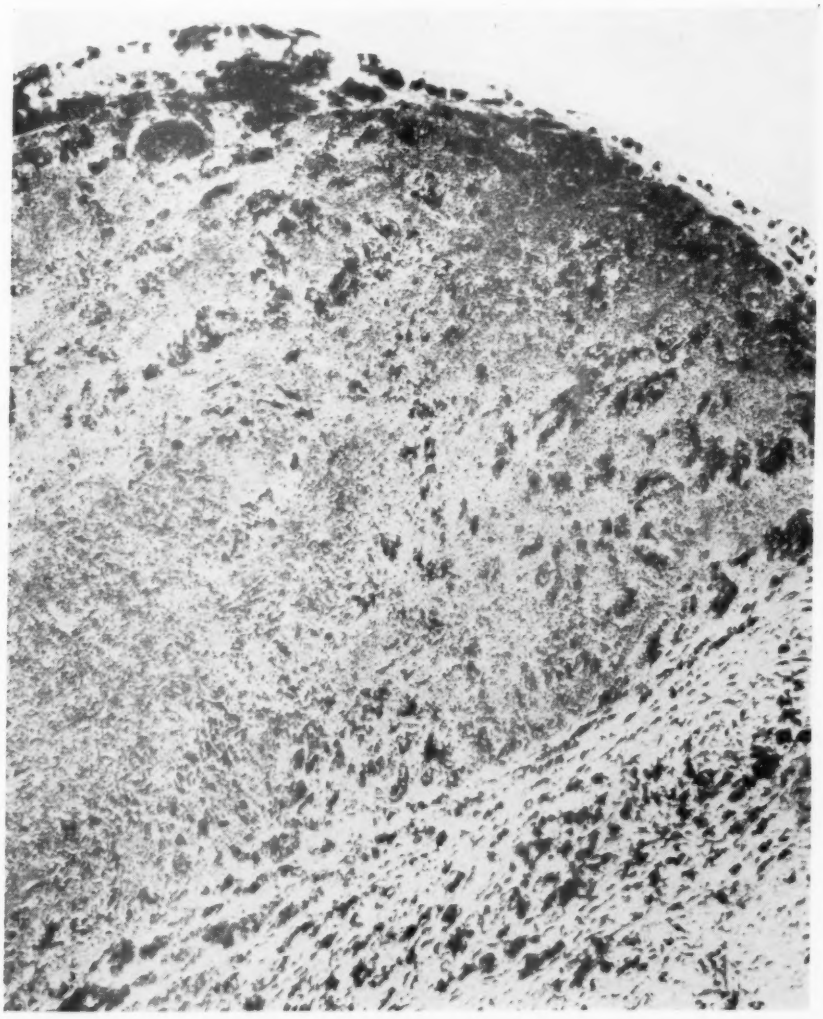

Fig. 3.—Intima and portion of underlying media of fresh graft from rabbit with induced arteriosclerosis contains abundant lipid (appearing black) and fibrosis. (Oil red O; ×60.)

no apparent increase in the ground substance, and, occasionally, only slight to moderate sclerosis within the media of the freeze-dried grafts. One revealed focal calcification. The fresh grafts, on the other hand, revealed marked fragmentation, lack of continuity, and even loss of elastic tissue fibers, particularly in those examples of aneurysm (Fig. 7). In addition, fibrosis of varying cellularity and an increase in ground substance were apparent within the medial zone. Some nuclei of smooth muscle cells were noted within the media. The

reticulum fibers of this zone were present in decreased numbers and lacked their usual orientation to these latter cells. Abundant intra- and extracellular lipid deposits were present within the media of the fresh grafts (Fig. 8). The adventitia of both types of grafts was replaced by relatively acellular connec-

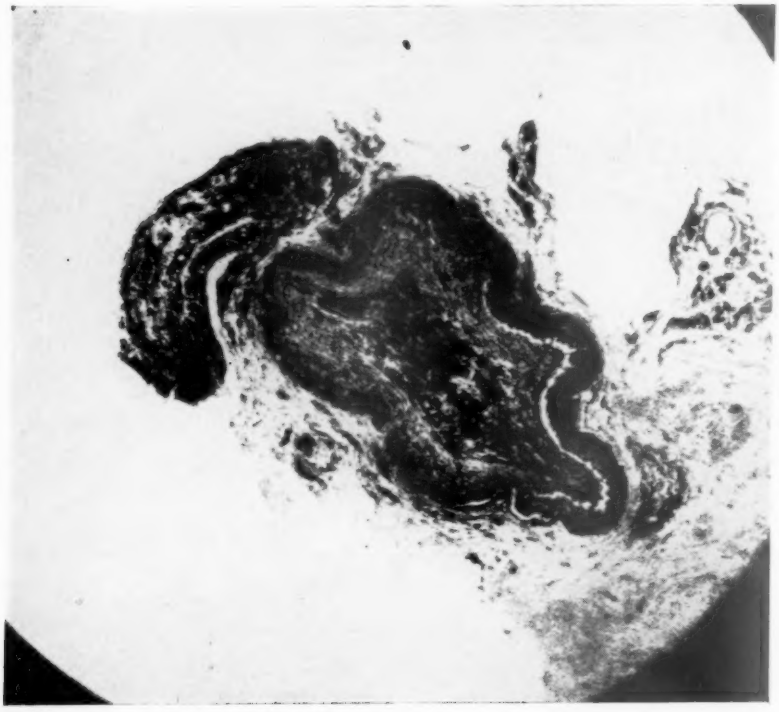

Fig. 4.—Cross section of fresh graft in rabbit with induced arteriosclerosis revealing occlusion of lumen by atheromatous plaque with abundant lipid (appearing black). (Oil red O; ×12.)

Fig. 5.—Lyophilized graft from rabbit with induced arteriosclerosis revealing abundant lipid (appearing black). (Oil red O; ×60.)

tive tissue derived from this layer of the host vessel, as well as the reparative zone at the lines of anastomosis. The newly formed adventitia was not unduly thick, and except in two examples of fresh grafts with aneurysm formation, it did not approximate the width of the media. Moderate vascularity was noted in the adventitia of both types of grafts, although it appeared more conspicuous in the fresh graft; and aggregates of lipophages were noted in the adventitia of some of the latter. Inflammatory reaction was conspicuously absent except in the one example of ruptured aneurysm. A moderate foreign body reaction was observed at the lines of anastomosis in all instances.

Fig. 6.—Aggregates of lipophages within media of lyophilized graft from rabbit with induced arteriosclerosis. (Verhoeff-Van Gieson; ×60.)

Portions of the host vessels not approximating the grafts revealed the classical microscopic picture of experimental cholesterol arteriosclerosis characterized by lipid cushions formed of intimal collections of lipophages and extracellular lipid as well as interspersed, delicate collagen and reticulum fibers. On several occasions focal calcification of these atheromatous plaques was evident. The degree of arteriosclerosis in these portions of the host vessels was less intense than that noted in the grafts. Medial accumulation of lipids was only rarely observed, and this was considered to be minimal. How-

ever, it was of interest to note that there was an increase in ground substance in the media of only that portion of the host vessel with a superimposed lipid cushion.

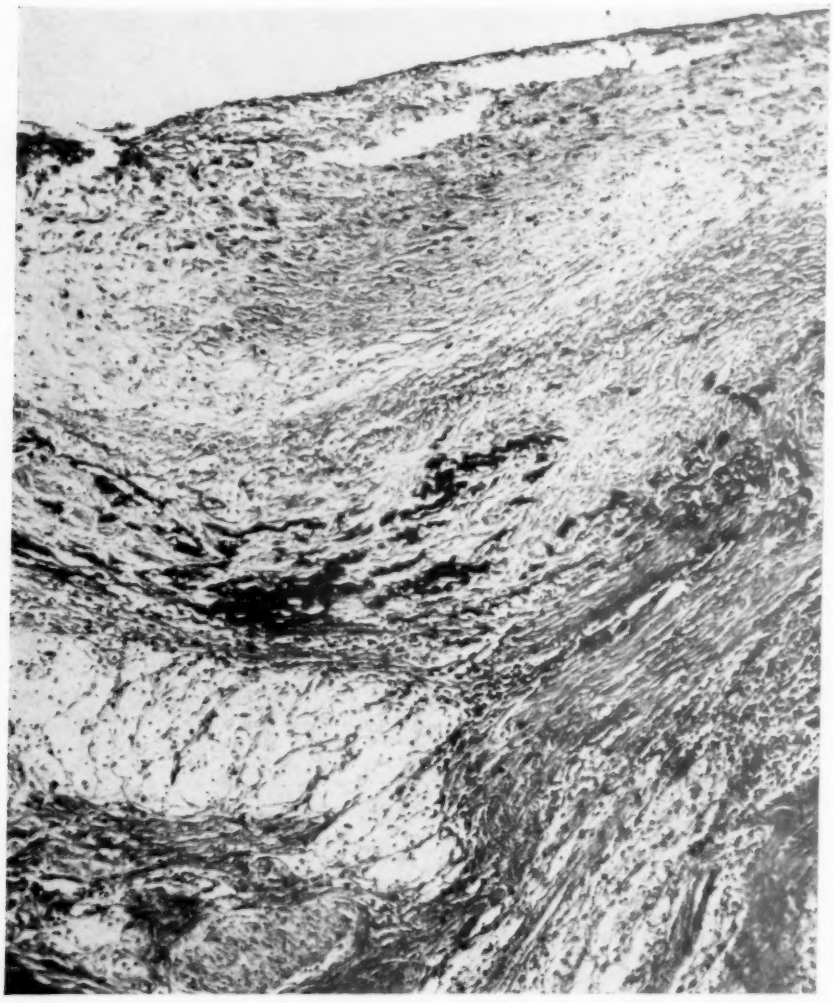

Fig. 7.—Section of wall of aneurysm in a fresh graft from a rabbit with induced arteriosclerosis. There is marked fibrosis and disruption of the elastica. Adventitial lipophages are also noted. (Verhoeff-Van Gieson; ×60.)

All of the sudanophilic material present within the grafts and host vessels reacted with the Schultz method for the identification of cholesterol and cholesterol esters. However, colorless birefringent crystals after digitonin precipitation were sparse, indicating that the lipid encountered was chiefly in the form of cholesterol esters. The free cholesterol demonstrated by digitonin precipitation was chiefly located in deeper zones of atheromatous change. Unsaturated lipids were apparently not present as indicated by the negative peracetic acid-Schiff reaction. There was no qualitative difference in the lipids observed in the freeze-dried or fresh homografts.

DISCUSSION

Although some of the changes which have been observed in homografts, such as fibrosis and calcification, are similar to those encountered in arteriosclerosis, evaluation of this latter in the homografts taken from the cholesterol fed rabbits was not difficult. The presence of lipids was noted only in the homografts from animals that received cholesterol. We have noted on occasion very sparse deposition of fine sudanophilic, nonbirefringent droplets which are negative with the Schultz procedure for cholesterol in the media and newly formed intima of fresh and lyophilized canine grafts after 12

Fig. 8.—Aggregates of lipophages in intima and media with disruption of elastica in fresh graft from a rabbit with induced arteriosclerosis. The reaction appears to be of greater intensity than that noted in Fig. 6. (Verhoeff-Van Gieson; ×60.)

months.[11] However, in no case were there aggregates of lipophages, or was the reaction of the intensity as noted in the rabbits with induced arteriosclerosis. Furthermore, we can find no other reference to the specific demonstration of such material in homografts studied in humans or dogs following transplantation. The presence of intra- and extracellular lipid within the

grafts also differentiated the arteriosclerotic lesions encountered from the spontaneous fibrocalcific plaques occasionally noted within the aortic media of the rabbit.[8]

That more severe arteriosclerotic changes were observed in the homografts than in the host vessels was not a totally unexpected finding. It has been known for some time that the development of experimental cholesterol arteriosclerosis in the rabbit is facilitated and enhanced when the vessels are damaged either by vasotoxic agents, such as nicotine,[1, 6] epinephrine,[1, 6] or viosterol,[16] or by mechanical means.[27, 28] Certainly, from their morphologic appearance, as well as from tissue culture studies, fresh and lyophilized homografts are to be considered as altered or "damaged" tissue. The occurrence of severe arteriosclerosis in the host vessel adjacent to the lines of anastomosis also reflects the stimulating effect of trauma attendant with aortic homografting upon the development of experimental arteriosclerosis.

It is apparent from the results of this study that in the rabbit with induced cholesterol arteriosclerosis the fresh homograft is more severely affected than grafts preserved by lyophilization. Aneurysmal dilatation and stenosis were encountered with alarming frequency in the former, whereas no animal with a lyophilized graft exhibited such a lesion. Since extreme caution was exercised to avoid utilizing homografts which might be considered to have a luminal diameter unequal to that of the host vessel, it is felt that this change is in all likelihood the result of the severe arteriosclerotic process induced in these rabbits. Support for this contention is offered by the work of Crawford and Levene[5] concerning arteriosclerosis and aneurysm formation in human aortas. Biologically, the fresh graft as evidenced by the growth of fibroblasts in tissue culture, might be considered viable, whereas the lyophilized graft has been demonstrated to be inert and incapable of growth.[20, 21] This may be a factor in the greater vascularity observed in fresh grafts. Such vascular arrangements undoubtedly play a role in the deposition of lipid. It was reflected in this study by finding more abundant lipid within the media and aggregates of lipophages in the adventitia of only the fresh grafts. Another factor of possible consequence in explaining this difference are the observations of Sawyer and Pate[24] concerning the reversal of electric potential in fresh grafts. The change of the normally negative intimal charge to positive could conceivably result in a stronger intimal affinity for lipoprotein molecules. The significance of this serum fraction in the development of arteriosclerosis has recently attracted much attention. Alteration in the electric potential of vessels has also been demonstrated to play a role in intimal thrombosis.[25] It is interesting to note that thrombus formation was observed only in the fresh grafts and in those animals with aneurysmal dilatation of the aorta. Whether such thrombi play an important initiating factor in the pathogenesis of the severe arteriosclerosis encountered, as might be considered from Duguid's[9] concepts of arteriosclerosis, cannot be stated with certainty, although it appears important in the progression of the lesions encountered in the fresh grafts.

It is not within the scope of this report to discuss the significance of these findings in regard to the pathogenesis of experimental cholesterol arteriosclerosis and their relationship to human arteriosclerosis. These shall be reported elsewhere. An appreciation of these results concerning the development of arteriosclerosis in both freeze-dried and fresh homografts in the rabbit shall be manifest only when sufficient time has elapsed to allow for an adequate evaluation of the fate of similar grafts in humans.

SUMMARY

A marked susceptibility to arteriosclerosis was observed in fresh and lyophilized aortic homografts in rabbits with experimental cholesterol arteriosclerosis. The degree of change noted in the grafts was greater than that manifest in other portions of the hosts' vessels.

Arteriosclerotic changes were more severe in fresh homografts than those preserved by lyophilization. Aneurysmal dilatation and stenosis were encountered only in fresh grafts. The mechanisms accounting for this discrepancy are discussed.

Because of the uncertain relationship between experimental cholesterol arteriosclerosis of the rabbit and human arteriosclerosis, the significance of these findings shall be apparent only when sufficient time has elapsed to allow for an adequate evaluation of the fate of human aortic homografts in this respect.

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CHLORPROMAZINE: A REPORT OF ONE DEATH AND EIGHT NEAR FATALITIES FOLLOWING ITS USE IN CONJUNCTION WITH SPINAL, EPIDURAL, AND CELIAC PLEXUS BLOCK

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CHLORPROMAZINE (Thorazine, Largactil, and so forth) is enjoying widespread use for many diseases and is being used as a panacea when other standard medical therapy fails. It is being administered to the surgical and obstetrical patient for its antiemetic and sedative effect. In most instances chlorpromazine is employed without cognizance being taken of its "adrenolyticlike" action on the cardiovascular system and the possible consequent lowering of the blood pressure. If this drug is used promiscuously or without recognition of *all* of its normal pharmacologic effects, serious complications and even death can be expected.

It will be recalled that only after a number of patients who had received cortisone (Cortone) or corticotropin (ACTH) therapy died for no apparent reason following anesthesia and surgery was it realized that these drugs had contributed to the deaths by suppressing function of the adrenal glands. It is now general knowledge that the patient who has been on such therapy for protracted periods of time and who has been withdrawn from that therapy within two to six months before an operation must be given adequate cortisone or corticotropin therapy preoperatively and postoperatively, or the stress of the anesthetic and the operation may be more than his body can tolerate.[5, 7, 9, 14, 15, 17] It has now become routine procedure at our institution for the anesthesiologist on preoperative rounds to inquire specifically if the patient has been on this type of therapy.

It is interesting to note that when a physician places a patient on cortisone or corticotropin therapy, he usually tells him that he has done so. However, physicians have not realized the potential hazard chlorpromazine therapy creates from the standpoint of the selection and administration of an anesthetic or the performance of a therapeutic or a diagnostic block procedure. They make no attempt to emphasize that this drug is being used and patients who are taking chlorpromazine seldom are informed of the drug's name. Therefore, it is time for a warning concerning a serious complication created by the use of chlorpromazine prior to surgery, obstetrical delivery, or therapeutic and diagnostic block procedures.

Chlorpromazine may, by itself, markedly lower blood pressure.[1, 2, 4, 6, 8, 10-12, 16, 18, 19] This may not result in a serious situation. But, if the effects of a sympathetic block from a spinal, epidural, or celiac plexus block are added to this action of chlorpromazine, the systolic blood pressure may fall to levels of 50 mm. Hg or lower. In the occasional case, no blood pressure at all can be detected. A fall in blood pressure of this nature does not respond to the use

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of the ordinary vasoconstrictor drugs in the usual doses. The only two drugs to which it will respond are phenylephrine (Neosynephrine) run in a very rapid drip and in a strong concentration or levarterenol (Levophed). We have observed three instances of this complication and have been informed of six others which occurred in the Seattle area.[3, 13] It was possible to elevate the blood pressure quickly enough to avoid untoward effects in all these cases except one. In the latter case the patient died, probably from the prolonged period of severe hypotension and the tissue hypoxia which accompanied it.

The following three cases are examples of the problem.

CASE 1.—The surgeon had seen a 49-year-old white woman at home and placed her on chlorpromazine because of nausea associated with an intestinal obstruction. The surgeon did not mention this to the anesthesiologist, nor was it recorded in the patient's chart. The patient was given an epidural block for surgery and a severe hypotension developed which was difficult to correct, and although the patient survived the surgical procedure, she succumbed in the immediate postoperative period.

CASE 2.—The anesthesiologist saw a 50-year-old white man on preoperative rounds at four o'clock in the afternoon. Later the surgeon visited the patient and found him quite disturbed concerning the operation and therefore ordered 25 mg. of chlorpromazine immediately and another 25 mg. at midnight. At seven o'clock the next morning, without a recheck of the chart, a spinal anesthetic was administered with a light dibucaine (Nupercaine) solution and the desired level of anesthesia to the second thoracic dermatome obtained. Almost immediately, the patient failed to respond to questioning, and the blood pressure fell from a preoperative level of 90/60 to one which was unobtainable. Four milligrams methoxamine (Vasoxyl) was given intravenously and no response was noted. This was followed by 3 mg. of phenylephrine intravenously and the blood pressure slowly crept back to 70/40. The patient's blood pressure was sustained for the rest of the operation and in the immediate postoperative period by an intravenous drip of an unusually concentrated phenylephrine solution (40 mg. in 1,000 c.c. of 5 per cent dextrose in distilled water). The patient's convalescence was uneventful, and no untoward result from the period of hypotension and the associated hypoxia was noted.

CASE 3.—A 59-year-old woman who had carcinoma of the common bile duct and was having severe, intractable pain was referred to one of the authors (D. C. M.). The internist called and made an appointment to have the patient given a splanchnic (celiac plexus) block with a local anesthetic agent as a diagnostic test prior to the injection of alcohol in that area. She had been placed on chlorpromazine, 25 mg. t.i.d., to help control pain. However, the referring physician did not mention this medication nor was it recorded on the chart when she was seen by the anesthesiologist. The chart was not reviewed when she was brought to the block room three hours later. Immediately after the block the patient's blood pressure dropped from a preoperative level of 130/80 to 45/0. Five milligrams of methoxamine intravenously raised the blood pressure to 70/40, but it fell again to 45/0 in 10 minutes. It was then again raised and maintained at 90/60 with an intravenous drip of phenylephrine solution (10 mg. in 1,000 c.c. of 5 per cent dextrose in distilled water). The heart rate was grossly irregular. The patient was rapidly digitalized and the heart rate reverted to a normal rhythm. The patient made an uneventful recovery. Immediately after the treatment of the hypotension the remark was made to the resident that the patient looked as if she had received chlorpromazine prior to the block. The chart was checked and it was quite embarrassing to find that this had been the case. The fact that the patient was receiving chlorpromazine had been recorded on the order sheet and the nurses' notes in the interim between the anesthesiologist's visit and the execution of the block.

Because such severe hypotension may be caused by chlorpromazine therapy, it should become standard procedure that every anesthesiologist, before

selecting the type of anesthetic to be used or prior to performing a therapeutic or diagnostic block: (1) question the patient specifically as to whether or not he has had chlorpromazine therapy; (2) consult the patient's chart immediately before beginning the procedure so that any last-minute information may be obtained concerning whether or not the patient has been or was after the anesthesiologist's visit placed on chlorpromazine; and (3) question the surgeon, the internist, the obstetrician, and the house staff caring for the patient as to whether or not the patient is or has recently received the drug. The surgeon, the internist, or the obstetrician should also make a specific effort to inform the anesthesiologist whenever chlorpromazine has been administered to a patient who is to undergo a regional block procedure.

It is hoped that this warning may be of value in avoiding the problem of severe hypotension associated with chlorpromazine therapy. If a patient has been on chlorpromazine therapy, a general anesthetic or a peripheral nerve block, that is, a brachial plexus block, a sciatic-femoral nerve block, a pudendal nerve block, local infiltration, and so forth, is indicated—not a spinal, epidural, or intercostal-celiac (splanchnic) block. Unless this warning is heeded, more cases of severe hypotension with instances of consequent death will surely result.

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SCALENE NODE EXCISION

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PRESENTATION of a statistical array documenting an already well-supported procedure is not the purpose of this paper. Daniels[1] in 1949 suggested the excision and examination of a definite group of lymph nodes as an aid in the diagnosis of obscure intrathoracic disease. Since that time, particularly among thoracic surgeons, the procedure has become popular and several reports concerning its use have appeared in the literature endorsing it enthusiastically. It is our experience, too, that the subject is frequently broached at medical meetings and symposia and in staff conferences and conversation.[2]

At these times one cannot help remarking the varied terminology the procedure has acquired in six years. Perhaps this has its origin in the literature where the terms subclavian lymph node biopsy,[8] deep cervical fat pad resection,[6] and scalene node biopsy,[4, 5] appear, apparently to describe the same procedure. Other commentators "explore the neck."[3] Additionally, the terms supraclavicular biopsy and superior mediastinal biopsy are heard.

It is unfortunate that, as far as the nation-wide journals are concerned, except for the case described by Weiss and associates,[8] the articles dealing with this procedure have all appeared in the thoracic literature, yet, certainly the procedure is one falling well within the purview of general surgery and is frequently performed by general surgeons who do not particularly interest themselves in the chest.

In the literature the procedure is universally described, starting with Daniels, himself, as being done through a phrenicectomy approach using a 2 to 3 cm. incision.[4, 5, 8] We feel this, too, has added some confusion to the subject of exactly what is to be removed at these procedures.

To suggest a more standard terminology, to present the anatomy and so demonstrate the rationale of the procedure, and to clarify an approach to the area, is the purpose of this article.

ANATOMY

No one has defined better than Daniels, himself, the anatomy of the structure to be removed. "The space is bounded below by the subclavian vein, medially by the internal jugular vein, and laterally by the omohyoid muscle.

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The floor of the space is formed by the scalenus anticus muscle with the phrenic nerve lying in its sheath.'' Covering the space, layer by layer, as one approaches it surgically are the skin, superficial fascia and platysma muscle, the

Fig. 1*A*.—The completed dissection as described with important structures labeled for orientation.

superficial investment of the clavicular head of the sternocleidomastoid by the deep cervical fascia, the clavicular head of the muscle and, lastly, its deep investment from the deep fascia.

The anatomic preparation shown in Figs. 1*A*, 1*B*, and 1*C* was prepared by one of us (F. E. F.) to demonstrate the structure which is to be removed.

After the routine curvilinear thoracic portion of an autopsy incision had been made, extending back somewhat further than usual on the shoulders, the skin flap and platysma were laid back in the plane of the deep cervical fascia to the level of the hyoid bone. The right pectoral and clavicular portions of

Fig. 1*B*.—The completed dissection.

the pectoralis major were divided and reflected to their humeral origin. The right clavicular and sternal heads of the sternocleidomastoid were divided and the muscle reflected superiorly. The right sternohyoid and sternothyroid muscles

were reflected superiorly with the medial head of the omohyoid which was divided. The clavicle was disarticulated at its joint with the sternum and its medial half together with a portion of the subclavius muscle and clavipectoral fascia were resected. The medial two to three inches of the first four ribs and

Fig. 1*C*.—The completed dissection projecting the anatomical location of the displaced innominate, jugular, and subclavian veins and the inferior portion of the scalene fat pad.

their costal cartilages were subperiosteally or subperichondrially resected. The remaining cartilages, right and left, were divided at their chondrosternal junctions and the sternum was removed. The mediastinal pleural reflection was identified and the mediastinal pleura and adjacent structures were bluntly

dissected from the great vessels and trachea and retracted laterally without entering the pleural cavity. The right innominate vein was divided and its jugular and subclavian tributaries drawn upward and laterally. At the same time the scalene fascia was partially exposed with the phrenic nerve by cutting transversely across its overlying fat pad at the level of the omohyoid crossing.

By referring to Fig. 1, the intimate association of the lymph nodes in this fat pad to the nodes of the superior mediastinum can be appreciated. These nodes then, actually lying in the angle of the confluence of the subclavian and internal jugular veins, beneath the superficial layer of the deep cervical fascia, on the surface of the fascia of the anterior scalene muscle, touching medially and inferiorly the common carotid and subclavian arteries are the nodes desired. They are imbedded in a pad of fat.

If one projects the line of the clavicle it is clear this is not entirely a supraclavicular area. In part it is retroclavicular. Additionally, the supraclavicular nodes may be taken to include almost any nodes in the inferior portions of the cervical triangles. Hence, the term supraclavicular biopsy should be abandoned. Similarly, retroclavicular would not be correct.

The nodes and fat are in as intimate relation to the jugular vein and carotid artery as they are to the subclavian vessels. Moreover, the term subclavian nodes may be equally well taken to mean those around the third part of the vessels where they join the axillary divisions. Carotid nodes could mean anything from the root of the neck to the skull. These terms, then, are not tenable.

Deep cervical fat pad resection anatomically localizes nothing nor does the statement "explore the neck."

Superior mediastinal biopsy or, better, transcervical superior mediastinal node biopsy has much to recommend it, but it does not exactly define the nodes or the approach.

In order to clearly define what is sought in these procedures, we feel the term scalene node biopsy or, better, scalene node excision, since biopsy implies only partial removal of a structure, is the terminology of choice. It clearly defines the objectives and focuses the attention of the operator inescapably on one field. He cannot err because of inaccuracy of anatomic terminology. This is the terminology used by Johnson and by Shefts[4, 5] and which has become standard at our hospital.

TECHNIQUE

We have one comment to make on technique as it is described. Most simply, the approach is, in general, that of a standard phrenicectomy. Daniels first pointed out that division of the clavicular head of the sternocleidomastoid at times will facilitate the procedure. Shefts pointed out the necessity for careful dissection. Parenthetically, we may comment that the relationships described between these nodes and the carotid, jugular, and subclavian vessels in the previous section emphasize the need for care. Likewise, the transverse cervical artery and vein cross through this fat pad.

It is somewhat remarkable, therefore, in view of the obvious necessity for adequate exposure to read that the procedure can be done through a 2 to 3 cm. incision. We feel that perhaps this has misled some surgeons as to exactly the nature of the procedure to be performed.

Fig. 2 illustrates our incision, colored by Mercurochrome, measured on a postoperative patient. This one was 6 cm. in length. Above it is diagrammed a 3 cm. incision beginning at the lateral border of the sternocleidomastoid. Below it a 2 cm. incision is drawn. We have measured the depths of the wounds after excision of the scalene nodes and it frequently is greater than 2.5 cm. and usually is at least 2 cm. It is hard for us to conceive how adequate exposure of this depth can be achieved through such small incisions. This may

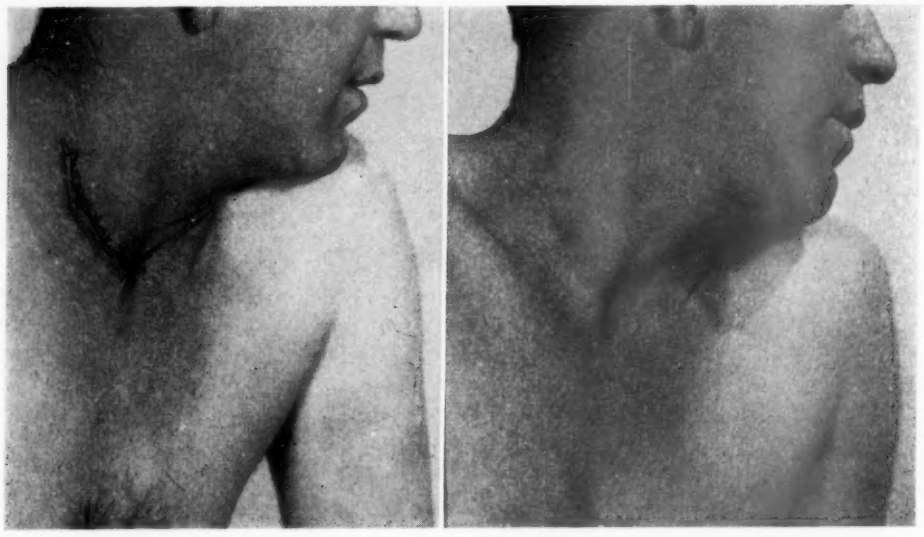
Fig. 2.—Illustrates the author's incision with a 3 cm. incision diagrammed above it and a 2 cm. incision drawn below.

well account for the disinclination of some surgeons to undertake the procedure. The length of the incision is not standard in our hands. We feel it should rest about three-fourths of an inch above the clavicle and extend from slightly lateral to the lateral border of the sternocleidomastoid to its sternal component or even beyond. Mobilization of skin flaps as in thyroidectomy will facilitate mobilization of the lateral head of the sternocleidomastoid for exposure. Frequently, it has been found that an approach between the two heads will result in better exposure than medial retraction of the lateral head. Nonabsorbable sutures have been used routinely, with layer closure, with good cosmetic results (Fig. 3).

The procedure scarcely inconveniences the patient at all. No preoperative preparation is necessary and no special postoperative precautions are advised.

In this we agree with Shefts, this is not a procedure for the intern. However, we feel even the junior assistant resident should approach it only under supervision. It is not entirely innocuous and, obviously, in unskilled hands, has even the potentiality of being fatal.

Shefts has pointed out the necessity of preserving portions of recovered nodes for culture. Particularly in Boeck's sarcoid, which is a diagnosis by exclusion, is this important. Granulomatous lesions should be stained by the acid-fast technique as well as by the Hotchkiss-McManus or periodic acid-Schiff stains. Reference is made to the article by Weed and Dahlin[7] for the method of handling biopsy specimens for bacteriologic examination.



A. *B.*

Fig. 3.—*A*, Scalene node excision, first postoperative day. *B*, One month postoperative.

DISCUSSION

The value of the procedure described by Daniels has been well demonstrated by other cited authors and particularly by Shefts' series of over two hundred such biopsies. It is indicated in any obscure intrathoracic disease and particularly in the diagnosis of mediastinal enlargements. It may save patients from the pain and expense of thoracotomy. It can be done by a competent surgeon in any hospital with a minimum of equipment and in a minimum of time.

Histoplasmosis, sarcoidosis, Hodgkin's disease, lymphosarcoma, tuberculosis, and metastatic carcinoma have all been diagnosed by this method and reported, when the diagnosis could not be made by other means except major exploratory surgery.

We have had experience with approximately fifty cases, and while it is not our intention to document them here we may add reticulum cell sarcoma to the list of lesions diagnosed. Our experience agrees with that of others that be-

tween 30 and 40 per cent of such biopsies will be rewarding. In our hands it has been the most valuable single diagnostic tool available in establishing the diagnosis of Boeck's sarcoid.

SUMMARY

1. There is a confusion in the literature concerning the terminology of a biopsy procedure for the diagnosis of obscure intrathoracic lesions.

2. We feel this confusion has misled some surgeons as to exactly the tissue to be removed.

3. The anatomy of the area in question is pictorially demonstrated, and the surgical approach discussed.

4. The universal adoption of the term "scalene node excision" in describing this procedure is urged to the exclusion of all other terminology.

5. The handling of the tissues removed for staining and bacteriology is discussed.

6. The results of our series and those of others are briefly referred to.

We wish to express our appreciation to Mr. John L. Templeton and Dr. Herman Bernhardt of the V. A. Hospital at Montgomery, Alabama, for taking the pictures of the dissection shown in this article and for placing facilities for the completion of the dissection at our disposal.

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ADDENDUM

Since our article was submitted for publication, an additional article on the subject by Connar has appeared in the literature which, in addition to presenting the anatomy of the lymph node group, draws attention to the work of Rouviere with reference to the lymphatic drainage of the lung and selection of the side of choice in doing scalene node excision. Connar likewise recommends a 5 to 7 cm. incision in the approach to the structure.*

*Connar, R. G.: Prescalene and Deep Cervical Lymph Node Biopsy, Surg., Gynec. & Obst. **101**: 733-743, 1955.

REPLACEMENT OF GASTRIC MUCOSA WITH AUTOGENOUS SKIN GRAFTS

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THE significant role that the acid secretion of the stomach plays in the development of peptic ulcer is generally recognized, although the fundamental pathogenesis remains obscure. The surgical attack upon peptic ulcer has been along three principal lines: drainage procedures, such as gastroenterostomy, which do not alter gastric secretion; removal of a portion of the stomach, partial gastrectomy; and elimination of the cephalic phase of gastric secretion by vagus nerve section. Of these approaches, only gastrectomy provides a direct attack upon the secretory epithelium. However, removal of a portion of the stomach is associated with certain undesirable consequences which are related to loss of capacity and motor function and to loss of the pyloric sphincter mechanism. The replacement of the gastric mucosa with some other epithelium has been studied as a direct attack upon the gastric secretory mechanism without significantly altering the fundamental motor functions of the stomach.

METHOD

Fourteen adult mongrel dogs were used in this experiment. A cervical esophagostomy was performed in the dogs by the technique of Ware and Howe.[3] A Levine tube was inserted through the esophagostomy for a distance of 3 to 4 cm. into the distal esophagus to assure patency. The tube was held in place by application of a padded plaster collar which prevented the animal from dislodging the tube. Oral feedings were started the following day and were tolerated without difficulty.

The definitive operation was carried out three to four days later. Intravenous Nembutal was employed for anesthesia. A split-thickness skin graft was cut to a depth of 0.008 to 0.010 inch from the anterior abdominal wall by means of a small Padgett dermatome. The grafts measured approximately 18 by 7 cm. The stomach was exposed through a longitudinal midline upper abdominal incision and was opened along the anterior surface by a 10 cm. incision about 3 cm. from and parallel to the greater curvature. Approximately 80 to 90 per cent of the gastric mucosa was stripped from the gastric wall from the esophagogastric junction to the antrum. This technique has been described by Longmire and associates.[2] After division of the skin graft into two equal parts, they were sutured to the bed of muscularis mucosa. One section was sutured along the greater curvature and the other along the lesser curvature on the posterior wall (Fig. 1). The grafts were secured at the corners by interrupted 2-0 cotton sutures, and 2-0 chromic catgut sutures were placed in a continuous fashion along the edges. A few single sutures of chromic catgut were used to secure the body of the skin grafts to the gastric wall. Small drainage incisions were made

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in the grafts (Fig. 1). The Levine tube which had been placed into the esophagostomy was advanced into the stomach, and a thin rubber balloon was attached to the end. The balloon was inflated with 100 to 200 c.c. of air in an effort to maintain pressure against the grafts. The gastrotomy incision was closed in two layers. Closure of the abdominal incision was performed with 2-0 cotton. The padded plaster collar was reapplied to prevent displacement of the tube. Intravenous infusions of 500 c.c. of 5 per cent dextrose in water and 200 to 300 c.c. of blood were given during the operative procedure. Penicillin and streptomycin were administered intramuscularly on the day of operation and for three days after operation. The dogs were not given oral feedings for five days. Intravenous therapy during this period consisted of 500 c.c. of 5 per cent dextrose in water daily. On the fifth day following operation, the balloon was deflated and the Levine tube was removed.

Fig. 1.—Appearance of thin split-thickness skin grafts at the time of application to the denuded gastric wall.

In 6 out of 7 dogs, the Levine tube and inflated balloon were regurgitated within the first twenty-four hours. As a consequence, the balloon tube and a drainage tube were brought out through a dependently placed gastrostomy which eliminated the necessity of a cervical esophagostomy.

Specimens of the grafted areas were obtained at intervals ranging from three to eleven weeks after the original operation. Initial biopsies were taken by means of laparotomy and gastrotomy under Nembutal anesthesia. Final biopsies and photographs were made at the time of sacrifice. Details are given in the following section.

RESULTS

Nine of the 14 dogs survived the procedure. Of the 5 deaths, 4 expired either during the operation or in the first twenty-four hours. One animal died on the seventh postoperative day with generalized peritonitis and gangrene of the entire stomach.

The 9 survivors were biopsied between three to seven weeks after the skin grafting. In all cases, grossly viable white skin was present, and contracture of the stomach had not occurred. The percentage of viable grafts varied from

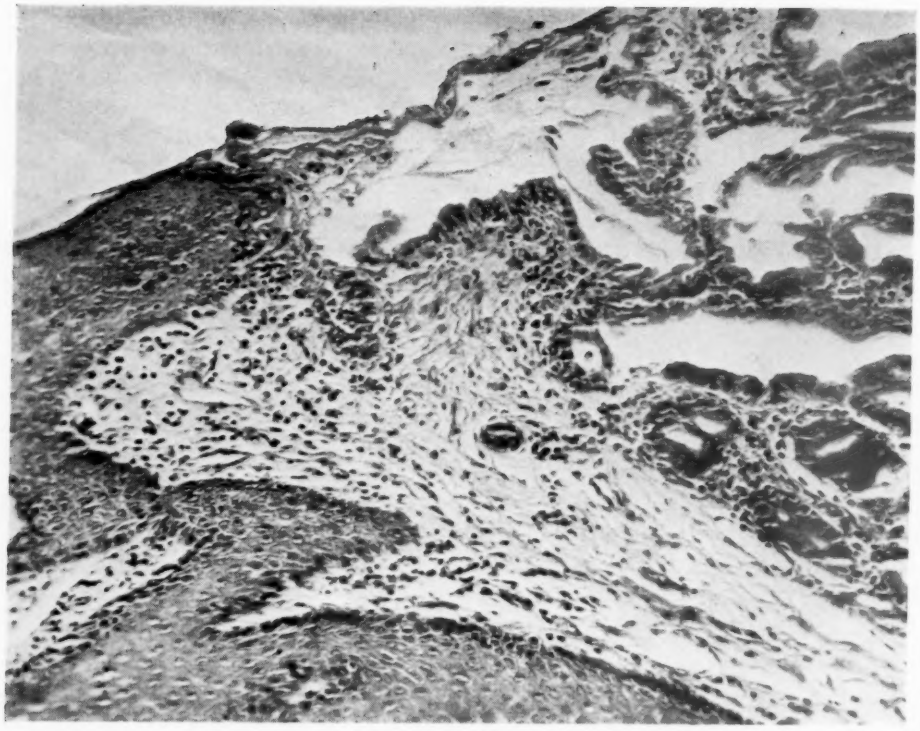

Fig. 2.—Photomicrograph of the junction between the split-thickness skin graft and gastric mucosa twenty-eight days after grafting from specimen obtained by biopsy (×144).

Fig. 3.—Photomicrograph of the dermal elements and cystic structures which are present when thick split-thickness skin grafts are used. Note the hair follicle, sweat gland, sebaceous glands, and cysts. Specimen obtained by open biopsy of gastric wall thirty-nine days after application of skin graft (×144).

one per cent in 4 animals to 25 to 80 per cent in the other 5 animals. Microscopic sections verified the gross findings of skin in all cases by the presence of stratified squamous epithelium. Immediately beneath this layer of epithelium was muscularis mucosa of the stomach. An abrupt transition took place between the epidermal and gastric mucosa (Fig. 2). Collections of macrophages and round cells with a few foreign body giant cells were found between the epithelial layer and the muscularis mucosa, but there was no other evidence of inflammatory reaction.

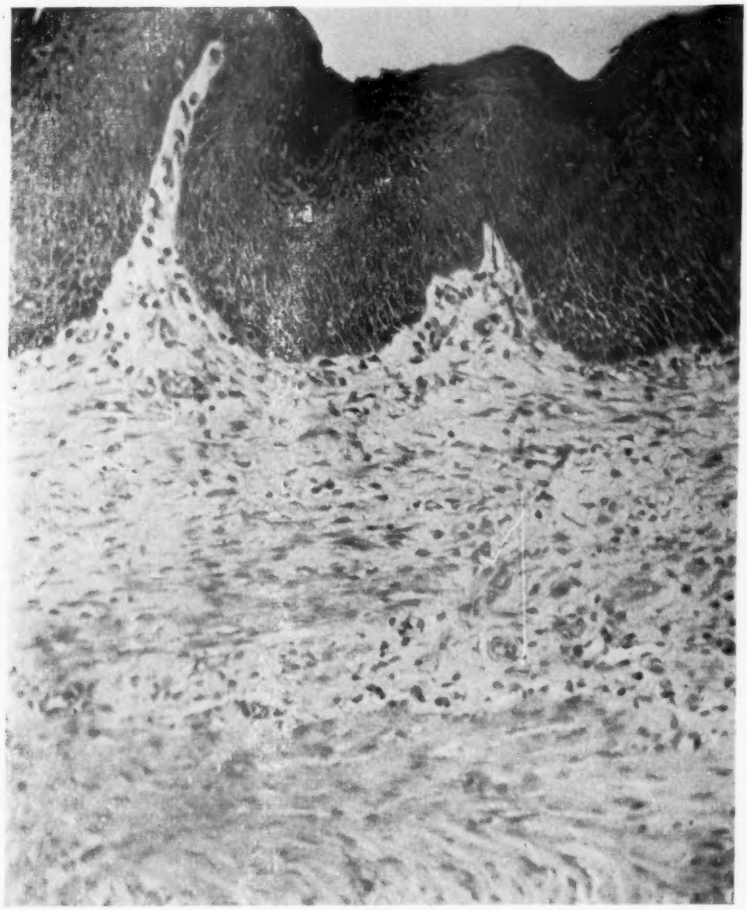

Fig. 4.—Photomicrograph of epidermis and muscularis mucosa of the gastric wall, which are seen when thin split-thickness skin grafts are used. Biopsy taken twenty-eight days after graft was applied (×144).

In the first 4 animals, grafts had been cut at 0.020 to 0.025 of an inch. Macroscopically, in these, 1 to 2 mm. bluish white subepithelial cysts were seen. Histologically, hair follicles, sebaceous glands, sweat glands, epithelial inclusion cysts, and cysts lined with columnar epithelium were identified (Fig. 3). Since thinner grafts have been cut, only epidermis has been seen under the microscope, and cysts have not been present grossly (Fig. 4).

A second biopsy was done four and one-half weeks after initial biopsy in 2 animals. There was no gross or microscopic difference in the appearance of

the grafted areas in this time interval. Evidence of digestion or ulcer formation in the stomach or grafted areas was not found.

DISCUSSION

Previous experiments demonstrated that excision of the mucosa of the canine stomach resulted in regeneration of the mucosa within three to eleven weeks.[2] The regenerated mucosa produced free hydrochloric acid in response to histamine which appeared to indicate that functional as well as histological repair had occurred. Although there seems to be a lack of this regenerative capacity in the cat and in man, the dog has been found to be more satisfactory for these experimental studies. The availability and size of dogs make them more practical.

Because excision of the gastric mucosa by stripping has been followed by regeneration of the mucosa, these experiments were initiated in an attempt to replace the gastric mucosa with autogenous skin grafts. Lippman and Longmire[1] have reported similar experiments in which the denuded gastric wall was covered with free grafts of jejunal mucosa. Skin was chosen for the present series of investigations because it is readily available in adequate quantities, is known to grow readily when grafted in other areas, and is resistant, perhaps more resistant than jejunum.

Certain inherent difficulties are present in this operative procedure. To insure a successful graft, there should be a minimum of motion of the recipient bed until the transplant is firmly adherent. This is difficult to achieve in the stomach because of involuntary contractile activity. Recently, vagotomy has been utilized in an attempt to overcome the problem of motion.

Prevention of hematoma formation beneath the graft has been less difficult than was anticipated. Although bleeding has been brisk during the process of stripping, hemostasis has been obtained by application of warm moist sponges. Concern was felt for the possibility of later accumulation of gastric secretion beneath the grafts from islands of residual gastric mucosa. This does not appear to have occurred to a significant degree, although the present experience is inadequate to determine this with certainty. Approximation of the graft to the concave surface of the gastric wall was a consideration that prompted the employment of the inflated intragastric balloon, as well as the placement of sutures through the central portion of the graft and the stomach wall. The occurrence of gangrene of the stomach in one animal was probably related to extensive distension of the balloon. Lippman and Longmire[1] reported difficulties which they attributed to the gastric distension from the balloon. Immobilization of the grafted area remains a serious problem in this procedure.

From the gross and microscopic studies in the 9 surviving animals in this investigation, it would appear that autogenous split thickness skin grafts can be grafted to the denuded gastric wall. The absence of hair follicles, sebaceous glands, and epithelial cysts in the thin split-thickness grafts suggest that these are superior to the thicker grafts. In general, the percentage of successful transplantation has increased with experience, and the occurrence of 80 per cent success in one animal is encouraging. A longer period of observation will be

required to determine the resistance of the grafts and their ability to survive in the gastric lumen. Gastric capacity and secretory function require additional investigation.

SUMMARY

An experimental study has been pursued in which the gastric mucosa has been stripped from 80 to 90 per cent of the stomach of dogs and partially replaced with autogenous split-thickness skin grafts. Fourteen animals were used, 9 of which survived the operative procedure. Viable skin was present in all survivors. The percentage of viable grafts varied from 1 per cent in 4 animals to 25 to 80 per cent in 5 animals.

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ADENOCARCINOMA OF THE VERMIFORM APPENDIX

A Case Presentation and Review of the Literature

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INTRODUCTION

CARCINOMA of the appendix has been divided into three histologic types for identification.[33] Carcinoids are the most common and least malignant. Most of the symptoms of the carcinoid type are secondary to the mechanical effect of obstruction. These tumors, however, do have marked local invasive properties and a slight tendency to metastasize from the appendix. Malignant mucoceles are the next most common type of appendiceal carcinoma. Complications of malignant mucocele occur from pseudomyxomatous peritoneal implants following rupture of the lesion into the peritoneal cavity. Distant lymphatic or blood-borne metastasis does not occur in this condition. The least common variety of carcinoma of the appendix is the adenocarcinoma of the colonic type. It resembles the ordinary colonic carcinoma in behavior, spreading by lymphatics and veins.

Uihlein and McDonald[31] found that of 144 carcinomas of the appendix removed surgically at the Mayo Clinic during the thirty-one years prior to 1941, 127 (88.2 per cent) were of the carcinoid type, 12 (8.3 per cent) were of the malignant mucocele type, and 5 (3.5 per cent) were of the colonic type. Between 1941 and 1949 seventeen additional malignant mucoceles and four additional colonic type carcinomas were encountered. Ehrlich and Hunter[7] reviewed 813 tumors of the gastrointestinal tract arising in Army personnel between the ages of eighteen and thirty-eight. There were 441 carcinomas in this group. Five were colonic type adenocarcinoma of the appendix.

In reviewing 2,301 appendectomies performed at this hospital between 1948 and 1954, 1 to 2 per cent showed neoplastic changes as follows: neuroma of appendix, 23; carcinoid of appendix, 3; unclassified tumor, 1; adenocarcinoma, colonic type, 1.

The case to be presented in this paper represents the first report of colonic type adenocarcinoma of the appendix given by the Department of Pathology. Histologically, however, it differs slightly from the classical description of colonic type adenocarcinoma in that the cells were extremely well differentiated and formed uniform nests. As is true in most cases of appendiceal carcinoma, this patient presented the clinical picture of acute appendicitis. The symp-

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tomatology may be produced by one of several mechanisms[4]: (1) obstruction of the lumen of the appendix by neoplastic tissue, (2) infiltration with perforation of the appendiceal wall, (3) obstruction of the lymphatic supply, or (4) obstruction of the vascular supply.

CASE REPORT

Mr. B. B., MH No. 25785, a 43-year-old white man, entered for the first time on Aug. 19, 1954, with a chief complaint of abdominal pain of two days' duration.

The patient had been well until two days prior to admission, at which time he developed a sudden dull epigastric pain which awakened him from sleep. Later in the day he developed crampy right lower quadrant pain along with the persistent epigastric pain which radiated to the back. There had been constipation, a low grade elevation in temperature, and anorexia noted since the onset of symptoms.

Past history, family history, and a review of systems was negative.

Physical examination revealed a well-developed, well-nourished, youthful appearing white man complaining of abdominal pain. Temperature was 101.4, pulse 84, respirations, 24, and blood pressure 120/84. Abdominal examination revealed tenderness and spasm to palpation in the right lower quadrant with rebound and cough tenderness in this area. Rectal examination was negative.

Laboratory findings were as follows: Hemogram showed hemoglobin 12.8 Gm., red blood cells 4.06 million, white blood cells 10,950, 63 per cent polymorphonuclear leukocytes, 7 per cent band forms, 33 per cent lymphocytes, 6 per cent monocytes, 1 per cent eosinophils. Urinalysis showed negative sugar, acetone, and albumin, sediment, 5-7 white blood cells per high power field, occasional red blood cell.

The preoperative diagnosis was acute appendicitis. The patient was operated upon the day of admission. An appendectomy was performed through a McBurney incision. At operation an elongated, distended, acutely inflamed, perforated appendix was found.

Pathologic Report.—

Gross: The appendix was 6.5 cm. long, distended, with mottled, hemorrhagic appearance and a thick plastic exudate over its surface. A perforation was present in the middle third of the appendix.

Microscopic: Sections between the base and the perforation revealed nests of glandular structures consisting of vacuolated cells showing considerable atypism and mitotic activity. All coats including serosa showed invasion, as did the perineural and larger lymphatic vessels. The serosa and submucosa at about 0.6 cm. from the proximal end contained tumor cell nests. There were no atypical changes noted distal to the perforation.

Pathologic diagnosis was mucous adenocarcinoma of appendix and acute, gangrenous perforated appendicitis.

On Aug. 27, 1954, a right hemicolectomy with ileotransverse colostomy was performed. Two small pericecal abscesses at the site of previous appendectomy were noted at operation. No residual tumor was felt in the cecum or terminal ileum. The postoperative course was uneventful and the patient was discharged on Sept. 5, 1954. Six months postoperatively the patient was alive and well.

Pathological Report (Second Operation).—

Gross: Thirty-one centimeters of ileum to the ileocecal valve and 23 cm. of colon were removed. Several loops of ileum were adherent to the base of the cecum with numerous patches of plastic exudate and firm fibrous adhesions. The mesenteric fat was indurated with the base of the appendix in a mass of fat and granulation tissue. The ascending colon was hyperemic. Five centimeters from the distal resection line the mucosa of the transverse colon showed a flat mucosal excrescence 0.7 cm. in diameter and freely movable over the submucosa. There were several enlarged, hyperemic mesenteric nodes.

Microscopic: Multiple sections of the cecum and site of resection of the appendix failed to reveal residual tumor. The cecum and pericecal tissues showed acute and subacute granulomatous inflammation with epithelioid cells, foreign body giant cells, polymorphonuclear leukocytes, and chronic inflammatory cells. The regional lymph nodes were free of tumor. The mucosal plaque of the transverse colon showed an area of hyperchromatism, atypism, and mitosis in the surface epithelium but none beyond the basement membrane.

Pathologic diagnosis was pericecal peritonitis and abscess formation, and atypical mucosa hyperplasia of transverse colon.

METHOD

In order to determine the incidence, treatment, and prognosis of this condition, a survey of the American, Canadian, and British literature was made from the years 1930 to 1954. Only colonic type adenocarcinomas of the vermiform appendix were included in this series. An attempt was made to bring all follow-up studies of these cases up to date by personal communication with the original authors of the cases reported in the literature. A total of twenty-four letters was sent to the physicians whose cases were reported. Fourteen answers were received in which recent follow-up studies were available. Table I lists the reported cases of adenocarcinoma of the appendix from 1930 to the present time. A total of seventy-one cases have been reported. In order to make this series as complete as possible, 16 cases of preinvasive adenocarcinomas of the appendix have been included. Table II is a composite chart listing each case reported individually. Each case has been analyzed to show the age and sex of the patient, presenting symptoms, pathology, operative procedure, findings at operation, and follow-up studies.

TABLE I

AUTHOR	NUMBER OF CASES	YEAR REPORTED
Montgomery and Johnson[25]	1	1931
Frauenthal and Grausman[9]	1	1933
Rosenblatt and Robertson[26]	1	1936
Waugh and Findley[32]	1	1937
Schuldt[27]	1	1940
Wright-Smith[35]	1	1941
Bieren[1]	2	1941
Young and Wyman[36]	1	1942
Chomet[2]	2	1944
Crile and Glenn[5]	1	1947
Maisel and Foot[21]	1	1947
Ehrlich and Hunter[7]	5	1947
Lesnick and Miller[20]	5	1949
Lee and Blain[19]	1	1950
Marks and Whitaker[22]	1	1950
Hughes[15]	1	1951
Smith[29]	1	1951
Sillery[28]	2	1951
Hilsabeck, Judd and Woolner[14]	9	1951
*McCollum and Pund[24]	16	1951
French[10]	1	1952
McCampbell and Dickinson[23]	1	1952
Lawton and Ehrlich[17]	3	1952
Fleming[8]	1	1953
Le Brun[18]	1	1953
Tannhauser[30]	1	1953
Clarke and Simonds[3]	2	1953
Gerber, Mackles and Raab[11]	1	1954
Guarino and Chitwood[12]	1	1954
Knepper, Riddell and Carpenter[16]	1	1954
Dent[6]	3	1954
Niceberg, Feldman and Mandelberg	1	1955

*Carcinoma in situ (preinvasive adenocarcinoma of the appendix).

DISCUSSION

This study indicates that adenocarcinoma of the appendix is found more frequently in the male than in the female population. Of the 49 cases in which the sex was reported, there were 31 men and 18 women affected. This seems to comply with the generally accepted view that acute appendicitis occurs predominantly among men. The age incidence is recorded in Table III. The youngest patient presented was 26 and the oldest 79 years of age. The peak incidence occurred in the fifth, six, and seventh decades, with more than 80 per cent of the cases reported in patients over the age of 40 years.

In more than 50 per cent of the series the presenting history and physical findings were compatible with the diagnosis of acute appendicitis. Table IV lists the preoperative diagnosis or symptomatology.

In ten cases the diagnosis was made pathologically following appendectomy performed incidental to another major surgical procedure. Table V lists the preoperative diagnosis in these cases. The value of prophylactic appendectomy is once again established, and although the number of cases of adenocarcinoma is seemingly small, this malignancy should be kept in mind in any abdominal surgical procedure. There were, in addition, two instances in which the primary site of the pathology was discovered at post-mortem examination. One of these patients was admitted because of cachexia, the other was admitted complaining of joint pains and abdominal distention. It is interesting to note that in no instance was the diagnosis made or even suspected preoperatively. In all but a few cases, the diagnosis was not made until the specimen was examined by the pathologist.

Two major surgical procedures were performed when the diagnosis of adenocarcinoma of the appendix was established. In most instances an appendectomy had been performed primarily. In twelve cases a primary colectomy was performed in addition to appendectomy when the diagnosis was made at operation, or a secondary colectomy was performed following pathologic diagnosis. Tables VI and VII show the results of follow-up studies made on patients treated by appendectomy alone compared with those treated by appendectomy and colectomy. The causes of death have been subdivided to indicate deaths due to metastatic disease and deaths due to unrelated conditions. Cases have not been included if there was either evidence of invasion of adjacent structures at the time of the initial operation, or if preinvasive adenocarcinoma was found. Cases with mesenteric node involvement, however, have been included. Twenty-six cases treated by appendectomy alone have been collected in which follow-up studies were available. Of these, 7, or 26.9 per cent were dead of their disease within three years following operation. Of the twelve cases treated by appendectomy and colectomy in which follow-up studies were available, only one, or 8.3 per cent died of metastatic carcinoma. Pathologically, these cases showed evidence of invasion of tumor beyond the mucosa of the appendix.

In view of these findings, it is believed that the procedure of choice in the treatment of adenocarcinoma of the vermiform appendix is appendectomy and

TABLE II

PRESENTING SYMPTOMS	AGE AND SEX	PATHOLOGY (DEGREE OF INVASION)	OPERATIVE PROCEDURE	FINDINGS AT OPERATION	FOLLOW-UP	CAUSE OF DEATH
Acute appendicitis with mass	49; M	Muscularis and subserosa	Appendectomy	Abscess	2 years	Alive
Pelvic mass	43; F	Serosa at tip of appendix only	Oophorectomy; appendectomy	Ovarian cyst; apparently normal appendix	5 years	Alive
Acute appendicitis	60; M	Serosa	Appendectomy; excision of omentum	Subacute appendicitis	5½ years	Generalized carcinomatosis
Acute appendicitis	49; F		Appendectomy	Appendicitis	11 months	Metastatic cancer
Acute appendicitis	64; M		Appendectomy	Gelatinous mass in midportion of appendix; perforated appendix	17 months	Metastases to peritoneum
Generalized joint pains; abdominal distention	61; M	Pleura, lungs, mesenteric nodes; primary site discovered at autopsy				
Acute appendicitis	44; F		Appendectomy	Gangrenous appendix with abscess formation	3 days	Peritonitis
Acute appendicitis	49; F		Appendectomy	Gangrenous appendix with abscess formation	2 years	Generalized metastases
Acute appendicitis	36; M	Mucosa	Appendectomy; secondary right hemicolectomy	Gangrenous appendix	15 years	Alive
Acute appendicitis	40; M	Muscularis	Appendectomy	Retrocecal, enlarged, adherent appendix	No follow-up	
Acute appendicitis	65; M	Entire wall of appendix, outer muscular layer of cecum	Appendectomy; secondary right hemicolectomy	Ruptured appendix	No follow-up	
Acute appendicitis	48; M	Mucosa	I & D followed by appendectomy in 3 months	Appendiceal mass	3 months	Alive
Multiple polyposis of colon	35; F	Mucosa	Total colectomy	Multiple polyposis of colon	7 years	Alive

I & D = Incision and drainage.

Acute appendicitis	F	Distal 2/3 of appendix involved	Appendectomy	Acute appendicitis	3 years	Alive with local recurrence
Acute appendicitis	41; F		Appendectomy; partial resection of cecum	Distended appendix	28 months	Metastatic Krukenberg tumors to ovaries
Cachexia	51; M	Abdominal carcinomatosis, primary site discovered at autopsy				
Acute appendicitis	36; F	Muscularis	Appendectomy; secondary right hemicolectomy	Acute appendicitis	9 years	Alive
Appendiceal abscess	57; M	Invasion of terminal ileum and omentum	Primary right; hemicolectomy	Perforated carcinoma with walled-off abscess	33 months	Intestinal obstruction due to recurrence
Acute appendicitis	57; M	Muscularis	Appendectomy; secondary right hemicolectomy	Acute appendicitis with swelling at the base	7½ years	Alive
Acute appendicitis	73; M	Metastases to ileum and ascending colon	Appendectomy; right hemicolectomy; radical resection of abdominal wall and small bowel	Perforated appendix	2 years	Metastatic carcinoma
Mass in right lower quadrant with intestinal obstruction	40; F	Entire wall of appendix, mesenteric nodes involved; erosion of ileum	Primary right hemicolectomy	Tumor mass of appendix eroding into ileum which in turn had intussuscepted into cecum	5 years	Alive
Appendiceal abscess	72; M	Muscularis	Appendectomy	Appendiceal abscess	2 years	Alive
Acute appendicitis	55; M	Serosa of distal appendix only	Appendectomy	Acute appendicitis	14 years	Alive
Acute appendicitis	34; F	Mucosa of entire appendix	Appendectomy	Mucosa replaced by villous tumor	No follow-up	
Extracecal mass	69; F	Muscle	Appendectomy with partial cecectomy	Polypoid mass in appendix	10 years	Alive
Abdominal fistula	60; M	Fistula to abdomen	Right hemicolectomy; fistulectomy	Polypoid lesion at base of appendix with abdominal wall fistula	5½ years	Alive

TABLE II—CONT'D

PRESENTING SYMPTOMS	AGE AND SEX	PATHOLOGY (DEGREE OF INVASION)	OPERATIVE PROCEDURE	FINDINGS AT OPERATION	FOLLOW-UP	CAUSE OF DEATH
Myomata uteri	36; F	Muscle	Myomectomy routine appendectomy	Apparently normal appendix	14 years	Alive
Cecal carcinoma	42; M	Muscle, lymph node involvement; independent lésion of cecum	Primary right hemicolectomy	Carcinoma of cecum	3 months	Carcinoma of cecum
Cecal carcinoma		Muscle; independent lesion of cecum	Primary right hemicolectomy	Carcinoma of cecum	No follow-up	
Cholecystitis	50; M	Mucosa	Cholecystectomy; routine appendectomy	Apparently normal appendix	14 years	Hypertension?
Ulcer pain	46; M	Mucosa	Gastrectomy; routine appendectomy	Apparently normal appendix	9 years	Multiple sclerosis
Cholecystitis	51; F	Mucosa	Cholecystectomy; routine appendectomy	Apparently normal appendix	5 years	Alive
Cecal carcinoma	68; F	Mucosa; independent lesion of cecum	Primary right hemicolectomy	Cecal carcinoma	4 years	Metastatic carcinoma of breast
Acute appendicitis mass in right lower quadrant	79; M	Muscle	Appendectomy; inversion of perforated base	Tumor mass in midportion of appendix; cecum perforated at base of appendix	2 years	Cerebral vascular accident
Myocardial infarct; signs of acute appendicitis while in hospital	53; M		Appendectomy; secondary right hemicolectomy	Gangrenous appendix	4 years	Alive
Acute appendicitis	72; M	Serosa	Appendectomy	Acute appendicitis with perforation at base	7 weeks	Carcinomatosis
Appendiceal abscess	58; F	Serosa	Appendectomy; secondary right hemicolectomy	Evidence of previous appendiceal abscess	5 years	2 abdominal wall metastases removed locally; alive

Acute appendicitis	60; M	Mucosa	Appendectomy; secondary right hemicolectomy	Acute appendicitis	3½ years	Alive
Prolapse of uterus	42; F	Mucosa	Hysterectomy and routine appendectomy; secondary right hemicolectomy	Thickened appendix no inflammation	3 years	Alive
Appendiceal abscess	56; M	Muscle	Ileotransverse colostomy; secondary right hemicolectomy	Mass involving base of appendix	4 years	Recurrent carcinoma
Acute appendicitis	56; M	Serosa	Appendectomy	Acute appendicitis	1 year	Alive
Acute appendicitis	70; M	Mucosa	Appendectomy	Perforated gangrenous appendix	4 years	Alive
Acute appendicitis	53; M	Muscle	Appendectomy	Perforated gangrenous appendix	15 months	Alive
Perforated viscus with peritonitis	65; M	Subserosa	Appendectomy	Perforated appendix with pelvic abscess	10 months	Carcinomatosis
3 months history of right lower quadrant pain and constipation	66; M	Appendix, sigmoid, cecum, and bladder	Appendectomy with local excision of tumor mass	Mass involving cecum, sigmoid, and bladder	9 months	Alive firm mass noted in right lower quadrant
Acute appendicitis	26; F	Muscularis, mesenteric involvement	Appendectomy; secondary right hemicolectomy	Acute appendicitis	3 years	Alive
Pain in right groin	39; M	Muscularis	Appendectomy; negative reexploration 3 months later	Perforated appendix	5 months	Alive
Acute onset of right lower quadrant pain while in hospital for ASHD and hypertension	65; M	Muscularis	Appendectomy	Enlarged, red appendix	2 months	Acute myocardial infarction
Acute appendicitis	58; M	Muscularis	Appendectomy	Grossly normal appendix	2 months	Acute myocardial infarction
Acute appendicitis	43; M	Serosa; lymphatic vessels	Appendectomy; secondary right hemicolectomy	Perforated, gangrenous appendix	6 months	Alive

ASHD = Arteriosclerotic heart disease.

right hemicolectomy. This procedure should be done for all cases where pathologic examination reveals the presence of carcinoma beyond the appendiceal mucosa. Although the number of such cases is small, it appears that lesions

TABLE III

AGE IN YEARS	NUMBER OF CASES
20-29	1
30-39	6
40-49	13
50-59	12
60-69	11
70-79	5

TABLE IV

PREOPERATIVE SYMPTOMS	NUMBER OF CASES
Acute appendicitis	28
Appendiceal abscess	4
Indefinite right lower quadrant pain	2
Perforated viscus	1
Abdominal fistula	1
Indefinite right lower quadrant mass	1
Extracecal mass	1

TABLE V

PRE-OPERATIVE DIAGNOSIS	NUMBER OF CASES
Carcinoma of the cecum	3
Chronic cholecystitis	2
Duodenal ulcer	1
Ovarian cyst	1
Prolapsed uterus	1
Myomata of uterus	1
Multiple polyposis of colon	1

TABLE VI. APPENDECTOMY

YEARS FOLLOWED	NO. OF CASES	DIED OF METASTATIC DISEASE	DIED OF UNRELATED DISEASE	ALIVE
Less than 1	8	3	3	2
1-2	7	2	1	4
2-3	2	1		1
3-4	1			1
4-5	2			2
More than 5	6	1	2	3
Total	26	7	6	13

TABLE VII. APPENDECTOMY AND COLECTOMY

YEARS FOLLOWED	NO. OF CASES	DIED OF METASTATIC DISEASE	DIED OF UNRELATED DISEASE	ALIVE
Less than 1	1			1
1-2				
2-3	2			2
3-4	3	1		2
4-5	1			1
More than 5	5			5
Total	12	1	0	11

limited to the appendiceal mucosa may be satisfactorily treated by appendectomy alone. Until more studies become available, however, this is not recommended as curative surgery in patients able to tolerate primary or secondary right hemicolectomy.

CONCLUSIONS

1. Adenocarcinoma of the appendix has never been diagnosed preoperatively.
2. The majority of patients with adenocarcinoma of the appendix present with symptoms of acute appendicitis.
3. The procedure of choice when the diagnosis of adenocarcinoma of the appendix is made is appendectomy plus primary or secondary right hemicolectomy.
4. In patients with lesions limited to the appendiceal mucosa, appendectomy alone appears to be satisfactory treatment.

SUMMARY

1. A case of adenocarcinoma of the vermiform appendix has been presented.
2. All cases of adenocarcinoma of the appendix reported in the literature between the years 1930-1954 have been listed according to author and date reported.
3. The reported cases have been analyzed to show age and sex of patient, presenting symptoms, pathology, operative procedure, finding at operation, and follow-up studies.
4. Follow-up figures have been subdivided to show survival time, death from metastatic disease, and death from unrelated causes.
5. A procedure of choice has been suggested as treatment of adenocarcinoma of the appendix.

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Case Reports

RESPIRATORY ARREST THOUGHT TO BE DUE TO INTRAPERITONEAL NEOMYCIN

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NEOMYCIN is an antibiotic, discovered by Waksman and Lechevalier[10] in 1949 from a strain of streptomycetes, closely related to *Streptomycetes fradiae*. Since that time its broad use in intestinal antisepsis, as well as its topical use in the treatment of cutaneous pyogenic infections,[3] has continually increased. Poth,[5] Pulaski and Connell,[8] Davis and associates,[1] Mann and Schumer,[4] and others have shown the effectiveness of the rapid preparation of the bowel with neomycin when adequate mechanical cleansing was accomplished.

The articles mentioning the intraperitoneal use of neomycin are extremely rare and Poth's articles, as well as Waksman's Monogram on neomycin,[12] are outstanding. Poth demonstrated the effectiveness of neomycin, used intraperitoneally, in eliminating infection when it was introduced into the grossly contaminated peritoneal cavity of a mouse. In 1951, he wrote that 1 or 2 Gm. of neomycin in 1 per cent solution can safely be placed into the peritoneal cavity of the human.[5] In 1954, he wrote that 2 to 3 Gm. of 1 per cent solution of neomycin may be placed in the grossly contaminated peritoneal cavity at the beginning of the operation and an additional 1 Gm. may be added at the end of the operation, thus making a total of 4 Gm. of 1 per cent neomycin solution used intraperitoneally.[6] He placed the solution of 1 per cent neomycin into the opened peritoneal cavity and much of it was lost during the course of the exploration; the remaining portion of it was aspirated. Excellent results were obtained using the drug in this fashion. However, it was further mentioned that when neomycin had been given orally, less neomycin was tolerated by the intraperitoneal route.

Reports of the toxic manifestations of neomycin in the literature are confined mostly to nephrotoxic and ototoxic effects. Kadison et al.[2] found, in the early studies of neomycin, that 132 mg. of neomycin per kilogram of body weight, injected intraperitoneally, was well tolerated by mice. More recent preparations have proved to be more toxic. Waksman and associates[11] found the minimum lethal dose for intraperitoneal neomycin in mice to be 125 mg. per kilogram of body weight, while Spencer[9] found 116 mg. for this dosage. Poth, in commenting on the acute toxic reaction of intraperitoneal neomycin in

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animals, stated that "Acute toxicity manifests itself by respiratory arrest. We have maintained experimental animals for hours by artificial respiration following respiratory arrest induced by intraperitoneal neomycin."[7]

In the San Antonio community, although we have found neomycin to be very effective with no toxicity when used in the intestinal tract, we have found it to have a low margin of safety when used intraperitoneally. Doses of 1 gram in dilute solution intraperitoneally have given gratifying results. On the other hand, with the aid of the anesthetists, operating room supervisors, and surgeons, we have collected 4 cases which demonstrate various stages of respiratory arrest resulting from the intraperitoneal use of slightly larger doses of neomycin. None of these cases had more than the standard calculated intraperitoneal dose of neomycin. However, the neomycin was not aspirated from the peritoneal cavity. Two infants expired and two adults were saved only after prolonged efforts of the anesthetists, using artificial respiration. The cases occurred in different hospitals and the anesthetist in each case was a different physician who limited his work to anesthesia. The surgeon in each case was a different physician who limited his work to surgery. These cases were studied repeatedly by all concerned and a brief history of each case is given below.

CASE REPORT

The first case was that of a 4-month-old baby who had a sudden onset of cramping abdominal pain that occurred in recurrent episodes. This began in the night about four hours before surgery, but no vomiting occurred. Past history and family history were noncontributory. Physical examination revealed a well-nourished infant of four months in acute pain. Examination of the heart and lungs was negative. A large elongated mass could be felt in the left abdomen. Rectal examination revealed a mass and current jelly-like material remained on the examining finger. Physical examination was otherwise negative. The laboratory reports were essentially normal.

About one hour was required to carefully reduce a large ileocolic intussusception, manually. Five-tenths gram of dilute neomycin solution was placed in the peritoneal cavity as the peritoneum was closed, because the cecum had remained slightly dusky. Open-drop ether had been given for the anesthetic and the infant had had no difficulties in anesthesia. The baby ceased breathing within fifteen minutes after the neomycin had been placed in the peritoneal cavity. The anesthetist force-breathed for the infant for eight hours while the surgeon stood by in the event cardiac arrest developed. The blood pressure and pulse remained good until the baby expired eight hours later from complete respiratory arrest in spite of coramine and 50 c.c. of blood. The pathologist did an immediate autopsy and found no cause of death.

The second case was that of a 17-month-old infant who developed recurrent episodes of abdominal pain with nausea and vomiting about sixteen hours before surgery. Past history and family history were noncontributory. Physical examination revealed a slightly dehydrated infant weighing 25 pounds. The positive findings were confined to the abdomen which was rather rigid with a suggestive mass present in the right lower quadrant. Rectal examination was negative. The laboratory findings revealed a slight leukocytosis, and a small bowel distention was noted on x-ray examination; urine examination was negative.

Through a right pararectus incision, the abdomen was explored and a small bowel volvulus was found. About one hour and one-half was required to resect a 6 cm. section of gangrenous terminal ileum and to perform an anastomosis. The child withstood the procedure well and had no difficulty with a gas-oxygen-ether anesthetic. Five-tenths gram of neomycin in 50 c.c. of sterile water was placed in the peritoneal cavity while the abdomen was closed.

Within twenty minutes the baby ceased breathing, and prolonged efforts at artificial respiration were unsuccessful. The pulse and blood pressure remained normal until the baby expired of respiratory arrest.

The third case was that of a white woman, 28 years of age. She had had a typical history of a duodenal ulcer for three years, and developed a sudden severe epigastric pain. Her past history and family history were otherwise negative. Physical examination revealed a well-developed female in acute pain, but not in shock. The positive findings were confined to her abdomen which was rigid with maximum tenderness in the epigastrium. The pelvic and rectal examinations were negative. The roentgenogram taken with the patient in the upright position revealed air under the diaphragm. The other laboratory results were normal except for a slight leukocytosis.

Under gas-oxygen-ether anesthesia with atropine sulfate, grains 1/150, and morphine sulfate, grains 1/6, subcutaneously for premedication the abdomen was explored and a ruptured duodenal ulcer was found; at no time did the patient have difficulty with the anesthetic. The hole in the duodenum was easily closed, using two rows of interrupted 3-0 cotton sutures. Two grams of neomycin in 200 c.c. of sterile water was placed in the peritoneal cavity at the beginning of the operation, part of which washed out and part of which was aspirated. An additional 1 Gm. of dilute neomycin was placed in the abdomen while closing the peritoneum. The operation lasted about forty minutes and before the patient could be moved from the operating table, she ceased breathing. The anesthesiologist breathed for her for eight hours, after which time she was placed in an iron lung for an additional twenty-four hours. During the following twenty-four-hour period she required the help of the Emerson respirator at intervals, but after forty-eight hours she completely recovered. The blood pressure and pulse remained relatively normal throughout this entire episode.

The fourth case was that of a Negro man, 48 years of age, whose chief complaint was acute lower abdominal pain of some six hours' duration. He had been treated for diverticulitis previously; his past history and family history were otherwise noncontributory. Physical examination revealed a well-developed Negro man forty-eight years of age in acute abdominal pain, but not in shock. Positive findings were confined to his abdomen which was rigid in the lower half and had maximum tenderness in the left lower quadrant. Rectal examination was negative. Laboratory studies were essentially negative except for a leukocytosis.

Under gas-oxygen-ether anesthesia with atropine sulfate, grains 1/150, and morphine sulfate, grains 1/6 subcutaneously for premedication, the abdomen was opened and at no time did the anesthesiologist have any type of difficulty in administering the anesthetic. A ruptured diverticulum of the sigmoid colon was found. A colostomy was performed and the abdomen closed; the procedure required about forty-five minutes. The patient withstood the surgery well, but ceased breathing about twenty minutes after 3 Gm. of neomycin in dilute solution were placed in the peritoneal cavity. The anesthesiologist force-breathed for the patient with positive-pressure oxygen for over three hours while the blood pressure and pulse stayed relatively normal. Following a difficult convalescence, he completely recovered.

DISCUSSION

It is interesting to note that all four patients were of normal weight for their ages, in good physical condition preoperatively, except for their primary complaints, had short, effective operations and had absolutely no difficulties throughout their anesthesias. The respiratory arrest came on, in all cases, no later than twenty minutes after the neomycin was placed in the peritoneal cavity. Although the amount and dilution of neomycin placed in the peritoneal cavity was according to the routine dosage quoted in the literature, no attempt was made to aspirate the drug from the peritoneal cavity. In some of the cases, the dilute solution of neomycin was placed into the peritoneal cavity through

a catheter as the peritoneum was closed and therefore, remained there; in other cases it was placed in the open peritoneal cavity where much of it could be washed out. Possibly there has been some increase in toxicity in more recent preparations of neomycin, as suggested by the above-mentioned authors. Possibly humans do not tolerate intraperitoneal neomycin as readily as do experimental animals. However, in view of the results in the above four cases, it is felt that neomycin has a very small margin of safety in the peritoneal cavity, compared with a large margin of safety inside the intestinal tract. The margin of safety of intraperitoneal neomycin also is extremely narrow compared to the wide margin of safety of intraperitoneal penicillin. This circumstance further tends to give the surgeon a false sense of security.

SUMMARY

Four case reports, taken from different hospitals, are presented, demonstrating respiratory arrest. After a critical evaluation of the cases by all physicians concerned, it was thought to be due to the use of intraperitoneal neomycin. It is felt that, although the effective intraperitoneal dosage of neomycin is fairly safe in the adult when very soon aspirated, the safe dose of neomycin per pound of body weight, to remain inside the peritoneal cavity, has not yet been determined. It is emphasized that neomycin used for intestinal antisepsis inside the gastrointestinal tract has a relatively large margin of safety and is both effective and rapid in action.

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SURGICAL CORRECTION OF COARCTATION OF THE AORTA COMBINED WITH AORTIC VALVE REGURGITATION

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DURING the past ten years correction of coarctation of the aorta by resection of the anomalous part and closure of the defect by direct suture anastomosis or by vessel grafts has become standardized, and is no longer a surgical rarity. In a like manner, aortic valve regurgitation is being successfully treated, largely through the efforts of Dr. Charles Hufnagel,[1] who developed a plastic ball valve which is inserted into the descending aorta. However, the combination of the two operative procedures, designed to correct both aortic valve regurgitation and coarctation of the aorta within the same patient, is unusual, and for that reason is reported herein.

In May, 1954, Hufnagel[1] reported on the first patient whose aortic insufficiency and coarctation were managed by the placement of an autogenous graft and an artificial valve. Subsequently he has treated two additional patients in a similar fashion.[2]

CASE REPORTS

L. M., a 28-year-old man, was admitted to the Roper Hospital on Jan. 16, 1955, because of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. His history of cardiac difficulties began in December, 1953, with sudden chest and left arm pain, exertional dyspnea, and pedal edema. Prior to this time he was able to walk on all-day hunting trips, had worked full time lifting and handling heavy textile products in a cotton mill, and was a member of a National Guard organization. In March, 1954, he was admitted to the Spartanburg General Hospital because of severe congestive heart failure associated with hypertension. His condition responded well to diuretics and a digitalis preparation. He continued to have dyspnea on exertion, was forced to abandon his employment, and spent a great deal of time in bed. He was again admitted to the Spartanburg General Hospital in December, 1954, with increasing signs of heart failure associated with chest pain. A diagnosis of coarctation of the aorta was made and he was transferred to the Roper Hospital for surgical treatment. Examination at this time showed a well-nourished and well-developed young man who was slightly dyspneic while sitting in bed. The blood pressure was 220/80 in each arm. The brachiocephalic pulses were of "pistol shot" character and the pulsations in the lower limbs were barely palpable. The heart was enlarged and there was a marked precordial heave. A grade III blowing diastolic murmur was heard best at a point just to the right of the sternum in the third intercostal space, and to a lesser degree along the left sternal border. The liver was enlarged. Accessory studies were performed with the following results. X-ray examinations, including fluoroscopy and angiocardiograms, were consistent with a diagnosis of coarctation of the

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aorta with aortic valve insufficiency. Cardiac catheterization of the right side of the heart showed no abnormalities except a pressure of 70/10 mm. Hg in the right ventricle. Electrocardiographs showed delayed conduction time intervals and left ventricular hypertrophy. Routine blood and urine examinations were normal. Wassermann and Kline determinations were negative. The clinical diagnosis was coarctation of the aorta associated with aortic valve insufficiency which was either secondary to rupture of an aortic cusp or to rheumatic fever.

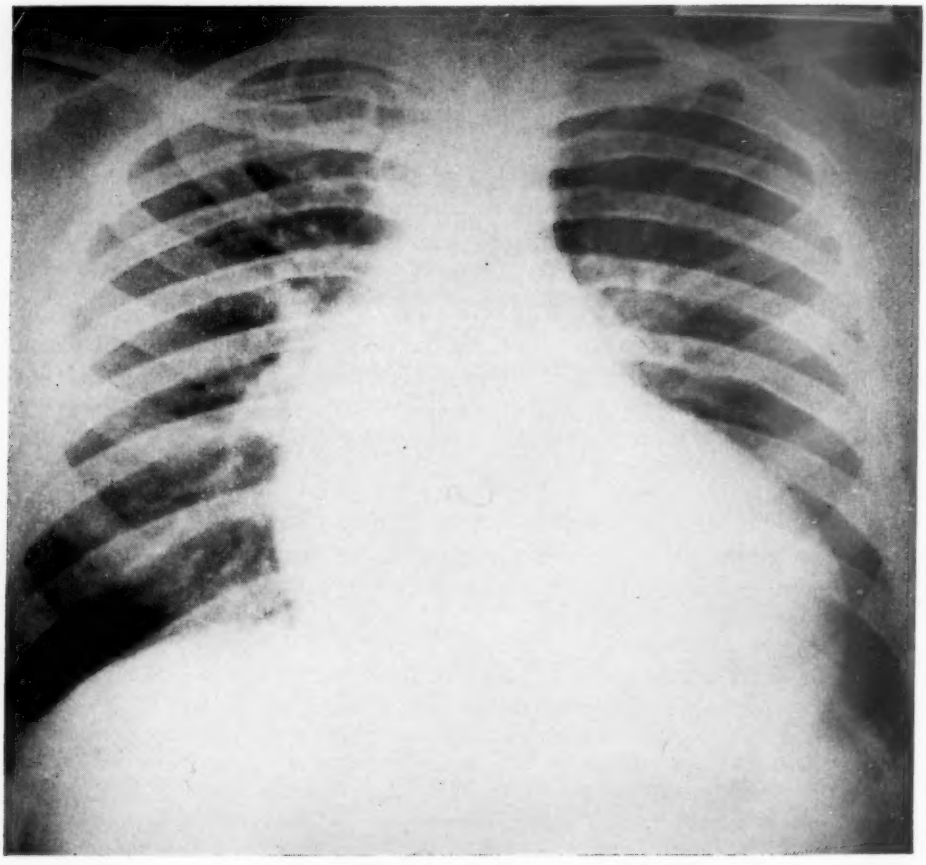

Fig. 1.—Roentgenogram of the chest made before operation showing cardiac enlargement and notched ribs.

On Jan. 24, 1955, the patient was taken to the operating room where, under light anesthesia consisting of Pentothal sodium, nitrous oxide, oxygen, and ether, administered by Dr. Laurie L. Brown, the left hemithorax was opened through the bed of the fifth rib. The pericardium and posterior pleural spaces were opened and the contents showed the following pertinent findings. All chambers of the heart were enlarged. No thrills were palpable over the valve areas. A ligamentum arteriosum extended between the left pulmonary artery and the narrowed portion of a coarctation of the aorta. The coarctation which arose just distal to the left subclavian artery was 0.5 cm. in diameter at the smallest segment, and extended distally into an aneurysm-like dilatation of the aorta. The arteries arising from the aorta proximal to the coarctation were enlarged. The aortic pulsations distal to the coarctation were markedly diminished. Because of the aortic valve regurgitation associated with the coarctation, plans were made to resect and replace the coarctation with a homograft attached to a Hufnagel plastic valve. Accord-

ingly, three sets of intercostal arteries were divided and the fourth set occluded with bulldog clamps. Aortic clamps were applied proximally at a level just distal to the origin of the left subclavian artery and distally below the level of the fourth intercostal vessels. The coarctation and the associated aortic aneurysm were resected. Because of the proximity of the coarctation to the origin of the left subclavian artery, the Hufnagel valve could not be safely clipped into place at this point. Instead an aortic homograft was attached to the proximal end of the Hufnagel valve and sutured to the proximally divided aorta. The distal end of the valve was attached to the distally divided aorta. A cuff of Orlon was sutured in place around the homograft just proximal to its junction with the artificial valve. After releasing the aortic clamps the ball-valve functioned properly and the pulsation in the aorta distal to the valve was normal. Leakage of blood at the proximal and distal anastomosis was controlled either with pressure or an additional suture. The patient withstood the operation satisfactorily. There were no significant alterations in the heart rhythm during the operation.

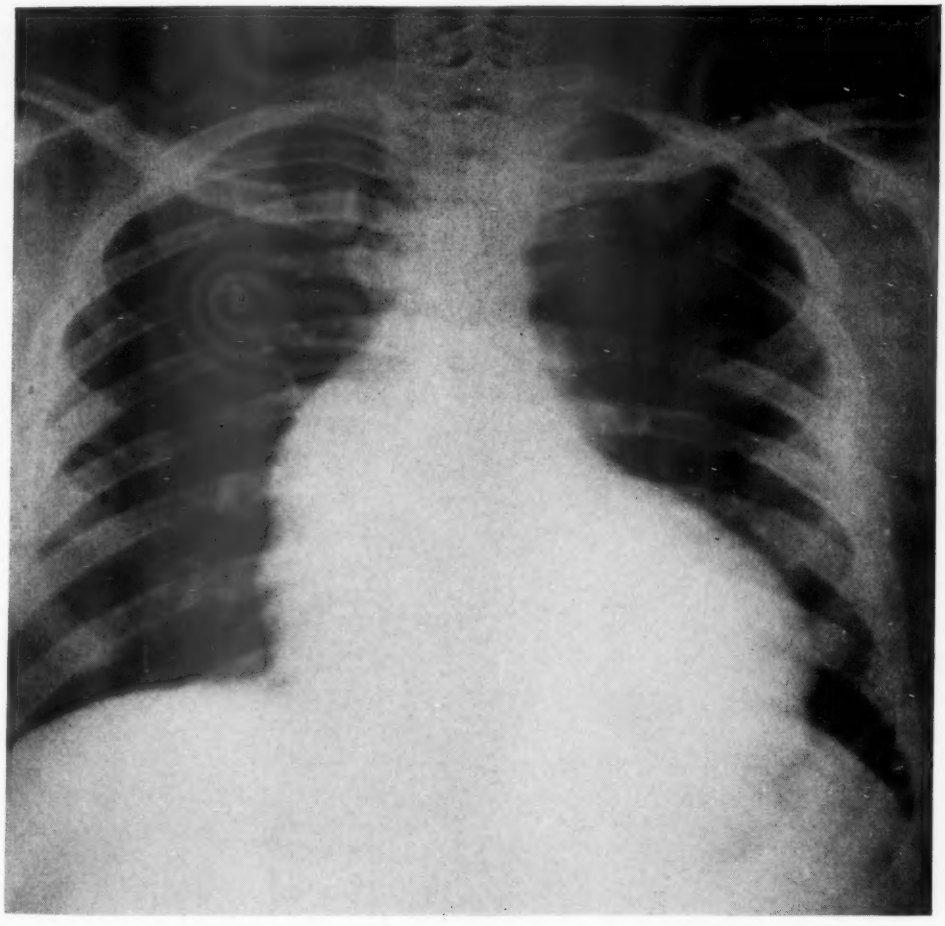

Fig. 2.—Roentgenogram of the chest made three months after operation showing diminution in the cardiac shadow. The fifth rib on the left has been resected.

The postoperative course was uncomplicated except for mild phlebitis at the site of a venesection of a superficial vein of the left leg. The blood pressure was 130/20 in the arm and 130/80 in the leg. He was discharged, much improved, two weeks after the operation.

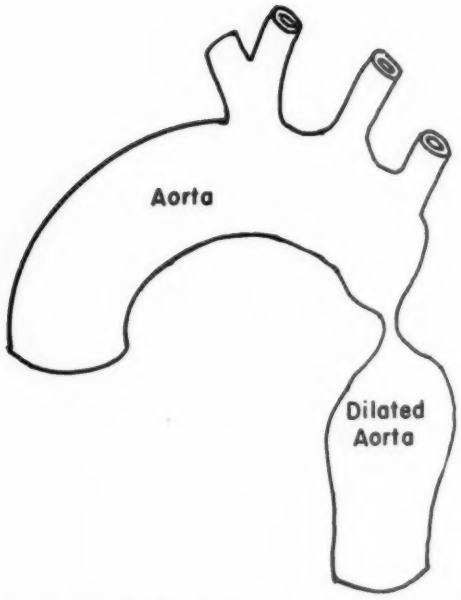

Fig. 3.—Sketch of the thoracic aorta before operation showing the coarctation and aneurysm of the descending aorta.

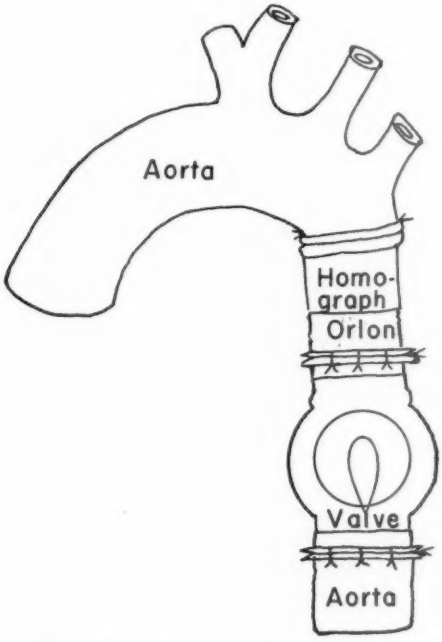

Fig. 4.—Sketch of the aorta after operation showing the Hufnagel valve and homograft which have been inserted following resection of the coarctation and aneurysm of the aorta. The Orlon cuff is placed around the aortic graft to prevent pooling of blood at the junction of the graft and the plastic valve.[2]

On a routine examination three months after the operation the patient stated that he remains ambulatory all day without difficulty, he no longer has claudication, and has not experienced dyspnea on moderate exertion. The valve noise is not troublesome to the patient. He plans to return to work on an eight-hour schedule. The heart is smaller in size, but the murmur of aortic insufficiency is unchanged. The blood pressure in the arm is 130/30 and the leg pulses are normal.

SUMMARY

A case history is presented of a 28-year-old man with aortic insufficiency associated with coarctation of the aorta. These disorders were treated simultaneously by excision of the coarctation and replacement of this segment of the aorta with a homograft and a Hufnagel aortic valve.

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MASSIVE ESOPHAGEAL BLEEDING IN A YOUNG GIRL, ASSOCIATED WITH ANOMALOUS DRAINAGE OF PORTAL VEIN

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ESOPHAGEAL bleeding associated with portal hypertension with intra- or extrahepatic changes are well documented in the literature. In adults the predominant pathology is cirrhosis of the liver. Madden[3] has shown, by injection and digestion methods, the disproportionate shrinkage of the hepatic veins in cirrhosis of the liver. Shumacker[6] has analyzed 21 children ranging in age from eleven months to fourteen years with massive gastrointestinal hemorrhages who had portal hypertension. In 20, no signs of hepatic involvement were noted by liver function tests and liver biopsies. One patient was found to have complete cavernous transformation of the portal vein and another, stenosis of the portal vein. We wish to report a case of repeated massive esophageal hemorrhages in a child presenting an anomalous drainage of the portal vein.

CASE REPORT

This 7-year-old Hawaiian Japanese girl was admitted to the Presbyterian Hospital of Chicago on a stretcher on June 24, 1954, after an emergency flight from Hawaii. She had an indwelling catheter in the right saphenous vein and fluids were constantly given throughout the trip, a matter of about sixteen hours. Two units of blood were carried along for emergency use and a doctor was in constant attendance.

In October, 1951, at the age of 4, she had developed severe gastrointestinal hemorrhage. Roentgenograms revealed extensive esophageal varicosities (Fig. 1, a). A diagnosis of cavernous thrombosis of the portal vein was made and she was sent to a hospital in the United States where a splenorenal shunt was successfully made. Following the shunt procedure the splenic vein pressure was reduced from 400 to 200 mm. of normal saline pressure. The patient made an uneventful recovery from surgery and was well for three months, although the esophagogram still showed extensive varicosities, as depicted in Fig. 1, b. Our qualms concerning the last finding were somewhat lessened by reports in the literature that esophageal varicosities do not always disappear after a successful shunting procedure. It was emphasized that the ultimate essential criterion was reduction of the portal pressure. In March, 1952, she had the first postoperative hemorrhage, which was repeated in November, 1953 (Fig. 1, c) and again in June, 1954. The severity of bleeding increased with each successive episode. The last bleeding could not be controlled and the child lapsed into coma time and again. All cutaneous veins were used and finally the jugular veins had to be used for transfusions. In desperation she was flown to Chicago.

The past history is irrelevant. The child was healthy and lived normally until the first hemorrhage.

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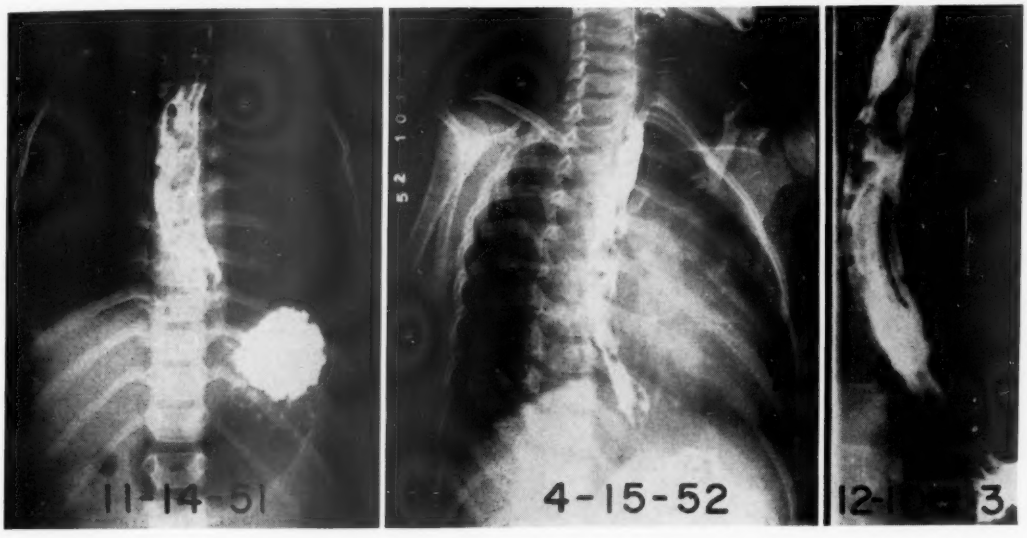
On entrance to the hospital the child was apathetic, pale, and appeared very ill. Her blood pressure was 116/72; pulse, 138; temperature 100° F. (R) and respirations 20. An intravenous needle was in the right saphenous vein. The previous left thoracoabdominal incision was well healed. There were no cutaneous varicosities, no ascites, and the liver was not palpable.

The laboratory findings on admission were: Hemoglobin, 4 Gm.; red blood cells, 1.32; white blood cells, 26,000; neutrophils, 8.8; Eosinophils, 1; Lymphocytes, 19; Monocytes, 2. Urine reaction was alkaline; specific gravity, 1.005; albumin, 0; sugar 0. The blood chemistry studies two days after admission were: non-protein nitrogen 51 (25-40 normal); total protein, 5.28 Gm.; albumin, 3.36 Gm.; globulin, 1.92 Gm.; NaCl, 648 mg. (560-620 normal); CO_2 combining power, 46 (55-75 normal). Six days after admission the prothrombin was 95 per cent of normal.



A. *B.* *C.*

Fig. 1.—Esophagograms of patient showing varices taken: *A*, At 4 years of age prior to spleno-renal shunt; *B*, four months after spleno-renal shunt. Varicosities are still present. First recurrent hemorrhage had occurred; *C*, two years after splenorenal shunt. Esophageal hemorrhages at this time were very severe.

While being studied and prepared for surgery she had a massive hemorrhage which was controlled by a Sangstaken tube and blood replacement.

At surgery on July 3, 1954, the portal area was exposed through a thoracoabdominal incision in the eighth right intercostal space. The diaphragm was partially incised. There were no dilated vessels or increased vascularity in the hepatic or gastrocolic omentum. The gastroesophageal junction was free of dilated veins. The liver appeared normal. The right kidney was enlarged compared to the left, but both felt normal to palpation. A one-half inch in diameter, normal-appearing portal vein was dissected from the retroduodenal area to just beneath the porta hepatis. A single vein was seen to join the portal vein just above the duodenum. Just beneath the porta hepatis, the portal vein made a right angle turn posteriorly and disappeared into the retroperitoneal tissue medial to the vena cava. At the convexity of the angulation a small fibrous band ascended into the liver at the porta hepatis. This appeared to be a rudimentary structure or remnant of the portal vein. There was a pressure of 340 mm. of normal saline present in the portal vein. The portal vein was sectioned at the most proximal point and an end-to-side portacaval anastomosis was performed using the everting type of suture. The fibrous band was ligated and divided. At the end of anastomosis, the portal pressure had dropped 60 mm. to 280 mm. of normal saline pressure. The anatomic findings noted at surgery are shown in Fig. 2.

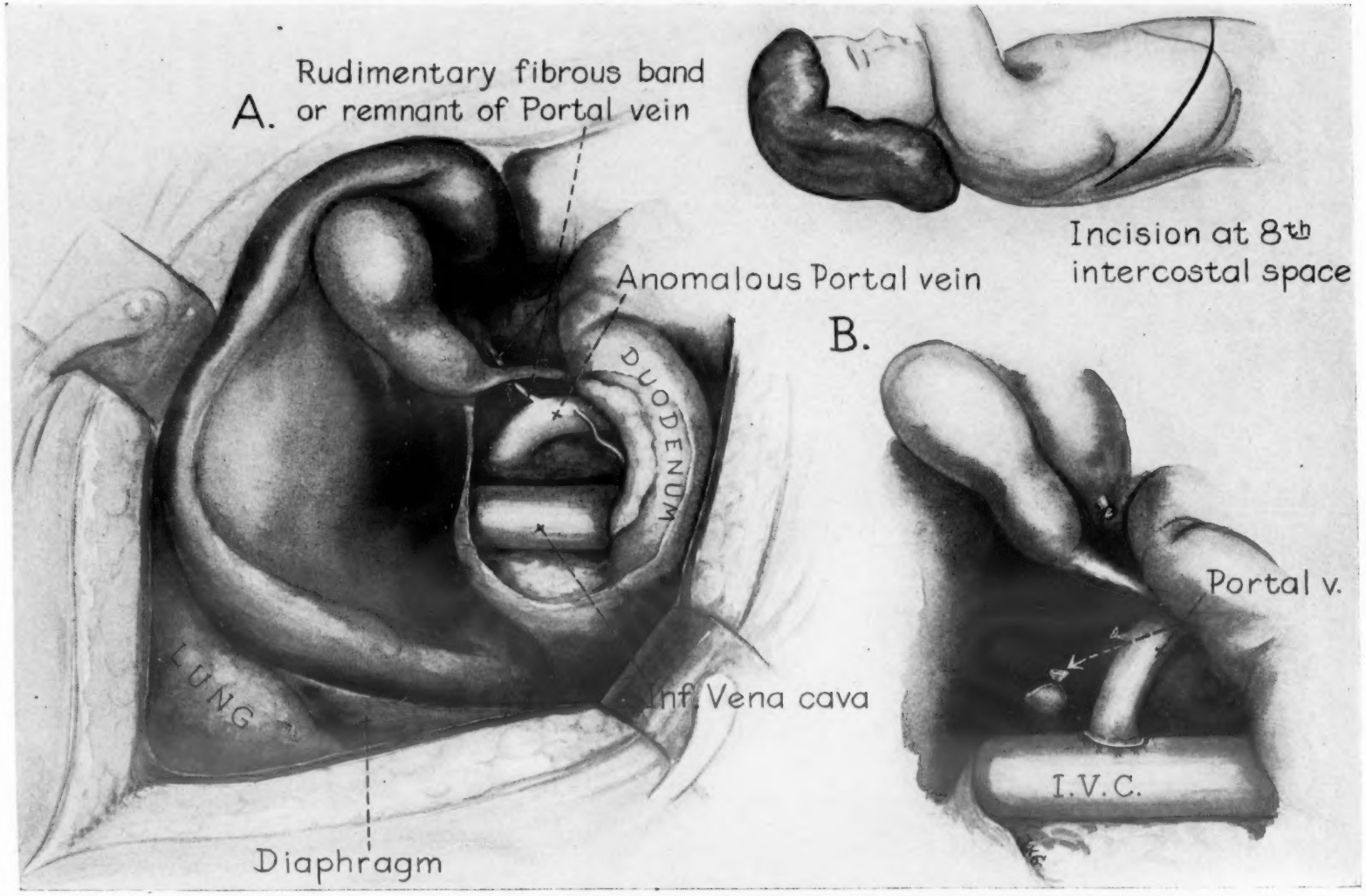


Fig. 2.—The drawings showing: *A*, The anomalous portal vein going behind the liver. A rudimentary fibrous band is in the location of the portal vein at the hilus of the liver; *B*, the method of portacaval anastomosis. The location of the thoracoabdominal approach is shown.

The postoperative course was uneventful and there was no episode of bleeding. However, the child ran an unexplained fever up to 102° F. at times. Because of this the discharge date from the hospital was delayed to 23 days after surgery. All hematologic and bacteriologic studies to account for the fever remained uninformative. At the time of discharge the patient had no complaints and appeared well.

Liver biopsy taken at surgery was considered normal histologically. Seventeen days after surgery the alkaline phosphatase, bilirubin, bromosulphalein and the proteins all were within normal limits. Roentgenogram of the esophagus taken twenty-three days after surgery showed varices similar to the preoperative examination. X-ray studies nine months after surgery (Fig. 3) showed the varices to be greatly diminished throughout the length of the esophagus.

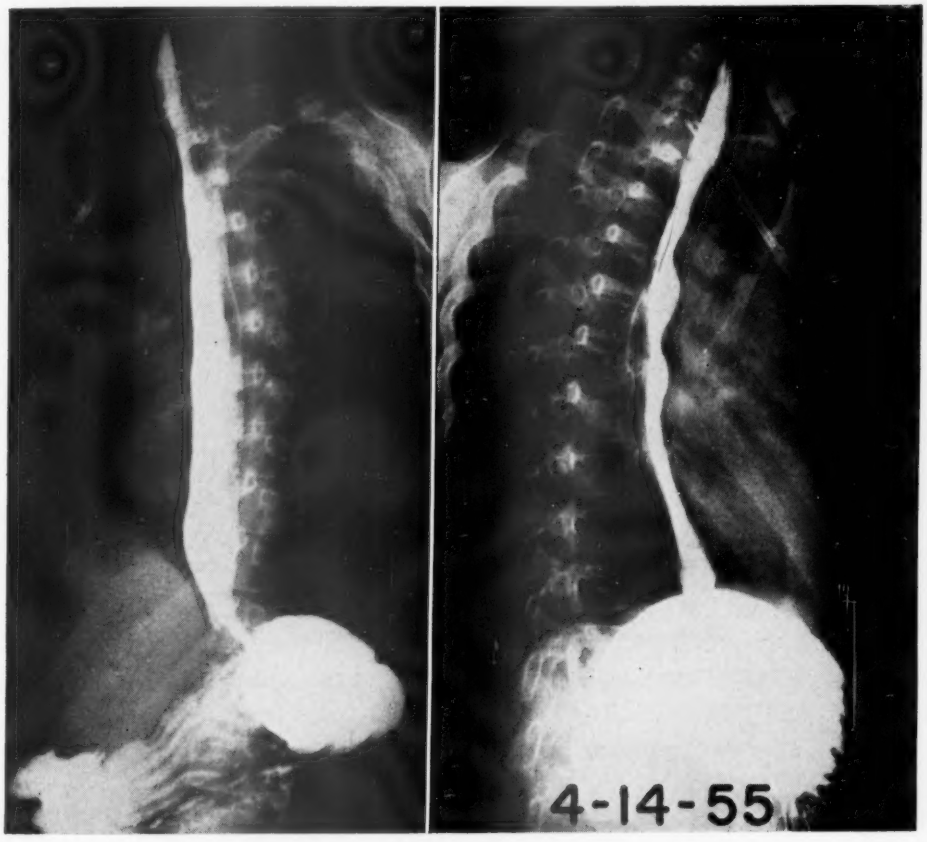


Fig. 3.—Esophagograms taken 9 months after anastomosis of an anomalous portal vein to the inferior vena cava. There is a definite lessening of the esophageal varices and the patient is clinically well.

DISCUSSION

The medical and surgical history has been presented of a child who had led a normal life to the age of 4 years and was then suddenly seized with severe esophageal bleeding. A splenorenal shunt was done which brought the portal vein pressure down from 400 to 200 mm. of normal saline. She did well for the next three months, after which severe hemorrhage occurred. Another surgical attempt was made to help the child two and one-half years after the splenorenal shunt. A portacaval shunt was done resulting in lowering of pressure from 340 mm. to 280 mm. of normal saline.

Fig. 2.—The drawings ... of the portal vein at the hilus of the liver; *B*, the method of portacaval anastomosis. The location of the thoracoabdominal approach is shown.

At the time of the second operative procedure an anomalous drainage of the portal vein was noted. It appeared that the anomalous portal vein followed a course behind the liver and possibly emptied into the azygos system, or esophageal veins, resulting in large esophageal varices. An angiogram of the portal system was purposely omitted due to the dire situation of the patient. Radiologic studies showed progressive diminution of the esophageal varices. The unexplained fever may have represented the systemic expression of thrombotic process in the varices.

The question arises as to the cause of the difference in size of the kidneys. Occlusion of the splenorenal shunt and renal atrophy of the left kidney may have occurred. No intravenous pyelogram or individual kidney function tests have been done to date. By palpation, the consistency of the left kidney was similar to that of the right.

SUMMARY

Esophageal hemorrhage based on an anomalous portal vein occurred in a girl of 7 years of age, whose bleeding was controlled by a splenorenal shunt for three months. A portacaval shunt performed two and one-half years after the splenorenal shunt has resulted in freedom from bleeding up to the present time (14 months). The esophagograms reveal a marked decrease of the varices. The child is now enjoying good health and to date has had no gastrointestinal complaints.

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Recent Advances in Surgery

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THE PAROTID GLAND: AN ANATOMIC STUDY

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THE question of whether the parotid gland is unilobar or bilobar and whether the facial nerve courses within the gland substance or occupies a separate tissue plane has never been settled definitely. The knowledge of this anatomy is not vital in itself but the possible influence it might have on the surgical approach to parotid neoplasms is considerable. It has long been known that benign mixed tumors of the parotid gland have a higher recurrence rate following apparently total excisions than any other benign tumors in the body. Large series place the rate of recurrence from a low of 11 per cent to a high of 42.5 per cent.[2, 4] Even if the lower figure is more valid, an 11 per cent recurrence rate of benign tumors is uniquely high. At present there is no adequate explanation for this phenomenon. The origins and growth patterns of mixed tumors are poorly understood, but there is little doubt that benign and malignant forms exist. Perhaps the recurrences of the benign forms are due to multicentric foci of origin as suggested by MacFarland[6] and others. It is also possible that the usual criteria for adequacy of resection do not apply in the region of the parotid gland. To evaluate the possibility that there are peculiarities of this region which interfere with total excision is the ultimate reason for this study. The status of the internal structure of the parotid gland and its relationship with the facial nerve branches are the points considered.

Many conscientious investigators, approaching the problem from different angles and with varying techniques, have accumulated conflicting data. The outstanding point of contention concerns the form of the gland; whether it is unilobar or bilobar, and whether the facial nerve branches actually pierce the substance of the gland, or lie in a tissue plane between the lobes. In 1917, McWhorter,[10] in presenting his work, stated that current English, French, and German textbooks of anatomy describe the gland as a single mass essentially, with various projections occupying the retromandibular fossa, and perforated by the facial nerve and its branches. But he found that in 1873 and 1901, Henle and his collaborators wrote that the parotid gland was made up of two distinct

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lobes divided by the facial nerve. McWhorter, having dissected 79 glands, 66 adult and 13 fetal and newborn, concluded that the gland was bilobar. His dissections led to the conclusion that the gland was essentially "H-shaped"; the upright limbs representing the superficial and deep lobes and the crossbar representing the narrow isthmus. He disagreed with Gregoire,[5] who, in 1912, described a bilobed structure with an isthmus of glandular tissue joining the two lobes at their superior poles. Gregoire reasoned that the "inverted V" appearance of the adult gland was due to obstruction by the base of the skull. He theorized that as the gland turned medially, further progress in this direction was blocked by the base of the skull which then caused the advancing gland to be deflected downward and medially. Rouviere and Cordier[11] in studying the sections of 31 and 51 mm. fetuses found that the deep lobe was double in origin; a portion bridging above the nerve, as described by Gregoire, and a portion bridging between the main branches of the nerve, as suggested by McWhorter. McCormack, Cauldwell, and Anson,[8] in 1945, in a study primarily directed at the facial nerve patterns, confirmed McWhorter's conclusions. In 1949, State[12] wrote that his dissections also supported McWhorter. Other surgeons, notably Bailey,[1] found that their operating-table observations bore out these contentions. Bailey, in the attempt to simplify the concept of two lobes, coined the term "parotid sandwich," the facial nerve branches in this case being the meat between the parotid bread slices. In 1946, Burford,[3] having dissected 11 adult normal parotids, found that in only 7 was the isthmus clearly defined. In the other cases this structure was ill-defined and inconstant. In only 4 of the 10 specimens where the bilobar nature was easily demonstrated did the nerve branches lie in the plane of cleavage between the lobes. In 5, one or more branches pierced the deep lobe tissue, and in one there were nerve branches within the superficial lobe. Also, in 3 specimens he found the nerve trunk prior to its primary division was embedded in one or the other lobes. At the end of his paper Burford stated that it was often difficult to define two lobes in the fixed specimens.

The first concrete evidence to be presented refuting the bilobar theory came from the work of McKenzie[9] in 1948. Obviously incensed by Bailey's blunt remarks about anatomists, McKenzie attacked the problem from another avenue. Before dissecting the specimens, he injected the duct system of the glands with a colored gelatinous material, making the ducts readily visible when cut across. He found that there were tiny ducts bridging between the lobes at other points than the main isthmus that could easily be missed by even the most careful dissector. To McKenzie belongs the credit for first utilizing the intrinsic duct system to establish the internal anatomy of the gland. None of his specimens (1 full-term fetus and 5 adults) revealed a simple bilobar arrangement. Instead of a single isthmus, there were many small "isthmi." He found that the bulk of the connecting tissue between the deep and superficial portions was largely within the main bifurcation of the nerve, but not all the deep tissue drained toward this isthmus. In each specimen small ducts were observed crossing this plane in all the interspaces of

the nerve branches. These small "isthmi" with their bridging ducts were more numerous in the region of the cervicofacial trunk. A few ducts were seen that drained a superficial lobule into a deeply placed collecting duct, whereas the predominating direction was from deep to superficial. McKenzie concluded that communication between the superficial and deep portions of the gland may occur through any gap in the nerve plexus. The manner in which the nerve interdigitates with the gland is not constant. He felt that a better analogy than the "parotid sandwich" of Bailey would be to compare the gland to a creeper vine "weaving itself into the meshes of a trellis-work fence."

Until this time, most studies on the gross anatomy of the gland were carried out by careful dissection in cadaver specimens. Although there can be no substitute for this form of investigation of the gland, certain errors may become manifest when the observations thus obtained are translated into descriptions of the undisturbed state. The creation of artificial tissue planes and false topography can be made very easily without the operator's awareness, despite the most careful work. It was to rule out this possible error that McKenzie injected colored gelatin into the duct system.

If the gland is essentially a two-lobed structure, then at some point the ducts from both lobes would have to converge, and if the nerve plane is the dividing line, then the nerve branches should be seen in the vicinity of the convergence. Our approach to this hypothesis was directed both toward the utilization of the undisturbed duct system, and the growth patterns of the gland itself. First, we injected an opaque material into the duct system of adult specimens with the gland undisturbed and by x-ray in three planes visualized the extent of the glandular tissue as indicated by the ducts. Second, an embryologic study was undertaken to elucidate the growth and migration of the involved structures, from their origins to their final positions.

Unfixed cadaveric heads were split in the mid-sagittal plane. The orifice of Stenson's duct was identified and a blunt hypodermic needle, usually a No. 19 or 20 gauge, was inserted into the duct. The specimen with the needle in place was immersed in a water bath where, by means of a heating coil, the temperature was kept constant at 50° C. The specimen was allowed to remain in the water bath for about one hour, so that its entire thickness would be at a constant temperature. The metal alloy called Cerrulow-117 which liquefies at 117° F. (47.2° C.) was heated to a temperature in excess of this critical level, and upon liquefaction, a small quantity was drawn up into an ordinary 10 c.c. Luer Lok syringe which was placed in the water bath with the specimen to maintain its fluidity. While under water, the filled syringe was carefully attached to the needle, and approximately 1.5 to 1.75 c.c. of the metal were injected into the gland. At the same time the needle was withdrawn, the orifice was firmly occluded by ordinary thumb pressure. The entire specimen was then carefully lifted out of the warm-water bath and plunged into a cold-water bath and allowed to remain there for several minutes. Within a few seconds the metal at Stenson's duct orifice, because of its superficial position, became solid. The specimen was then x-rayed in the antero-

posterior, lateral, and basilar views, after which it was placed in an earthen crock containing 20 per cent potassium hydroxide. When all the tissue was corroded away, usually in seven to ten days, a permanent metal cast of the duct system was left. Because of the scarcity of anatomic material, and the difficulties inherent in the process, only a few acceptable casts were obtained. The technical difficulties were many. There was wide variation in the size and shape of the ducts and, therefore, also in the intraductal capacity. Because there were no adequate guides in these specimens, the amount injected could not be individualized. If too little was injected, then the cast was sparse, and therefore could not be used to draw valid conclusions, since the number of ducts that escaped filling was unknown. Also, if too much material was injected, the gland became overdistended and assumed the "summer tree" appearance with so many closely packed radicles that accurate patterns could not be made out. McClenahan and Vogel[7] found that Cerrulow-117 in the liquid stage would enter vessels with lumina as small as 25 μ in diameter. An apparent advantage of using an alloy with a low melting point is that upon under- or overfilling, one could reheat the specimen and adjust the volume accordingly. This was not our experience, however, since a secondary adjustment of the volume always resulted in a weakened, unsatisfactory cast. Another serious problem was the digesting process. The weight of the tissue overlying the tiny radicles was in such ratio that the resulting cast rarely escaped without losing a considerable portion of its smaller branches. In many cases, the digesting process required several changes of solution with the resulting untoward manipulation of the cast. We attempted this same procedure on several full-term and premature newborn specimens, but, even with the aid of a dissecting microscope, were unable to probe the orifice of Stenson's duct. In spite of these difficulties, 20 glands were studied satisfactorily.

The intrinsic pattern of the gland as shown by the injection of the duct system reveals some interesting points. The films of these specimens, of course, do not show the nerve paths in relation to the ducts. However, in most cases it can be readily accepted that the nerve branches must be within the gland area because of the extent of the medial projection of the gland. In all cases it can be seen that the gland is composed primarily of a single mass of tissue, the bulk of which lies lateral to the masseter muscle and also occupies the lateral portion of the retromandibular space (Figs. 1 and 2). In each gland there is a portion which sweeps medially around the posterior border of the ramus of the mandible to occupy the space between the ramus and the lateral wall of the pharynx. However, this medial portion is still an integral part of the gland and no cleavage planes or divisions are evident in any of the views. The ducts which traverse the gland in a medial-lateral direction do not appear to converge on a single duct as might be expected if two lobar masses were present. Rather, the ducts appear to be branches of many larger ducts in all parts of the gland and occupy the full height of the gland at all points (Figs. 3 and 4). The roentgenograms tend to show a marked variation in the size of this medial portion.

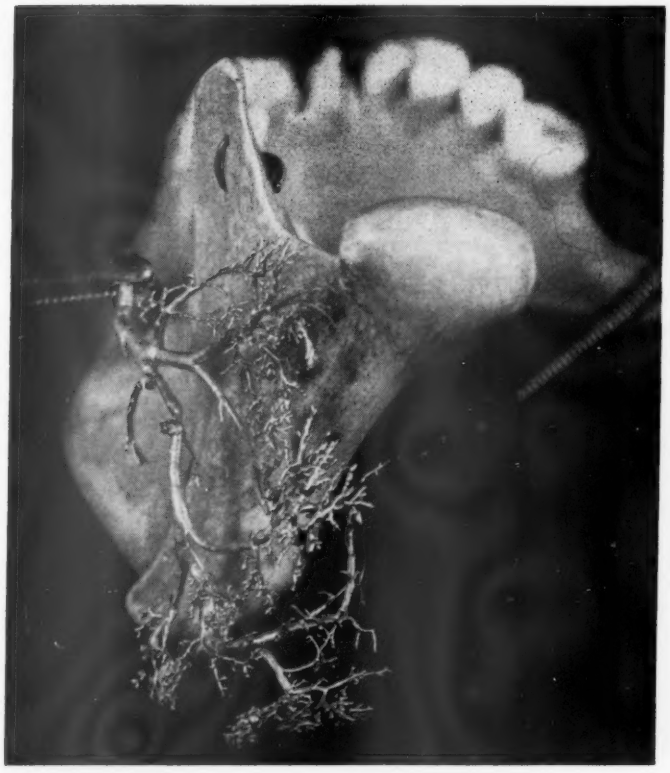
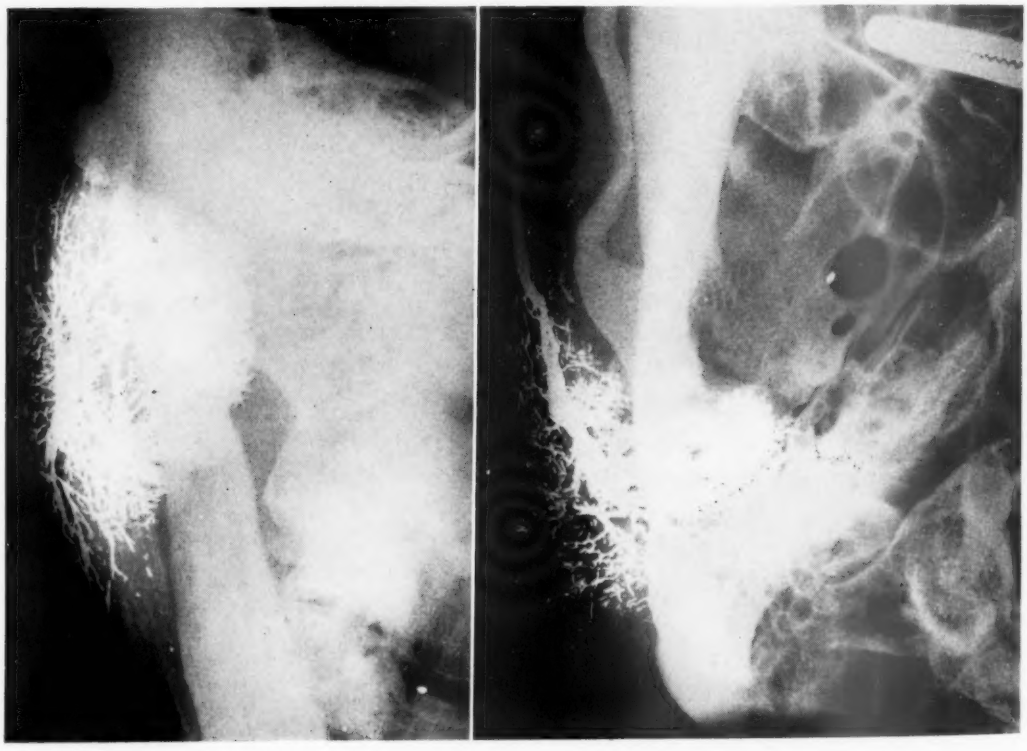


Fig. 1.—A metal cast of the left parotid duct system in its anatomic position is shown with a mandible. Note that the ducts sweeping medially occupy almost the entire height of the gland at all points.

Fig. 2.—A metal cast of the right parotid duct system in its anatomic position showing the absence of a narrowed "isthmus" area.

EMBRYOLOGY OF THE PAROTID GLAND AND FACIAL NERVE

There appears to be some disagreement in the literature as to the time of appearance of the parotid gland in the human embryo. Most textbooks of embryology state that it first appears in the sixth or seventh week and is definitely branching by the eighth or ninth week. The facial nerve itself can be seen in the 10 mm. embryo (sixth week) and the branches appear to be set by the time the embryo is 20 to 25 mm. (eighth week). The important fact in the relationship of the parotid gland to the facial nerve is the ultimate effect of one upon the other's final form. From the files of the Department of Embryology, Carnegie Institution of Washington, 26 embryos from 18.5 mm. to



A. *B.*

Fig. 3.—*A*, Anteroposterior view of right parotid duct system filled with a liquid metal. Note the large medial portion of the gland and the absence of an "isthmus." *B*, Basal view of same specimen showing the lateral (superficial) and the medial (deep) portions of the gland.

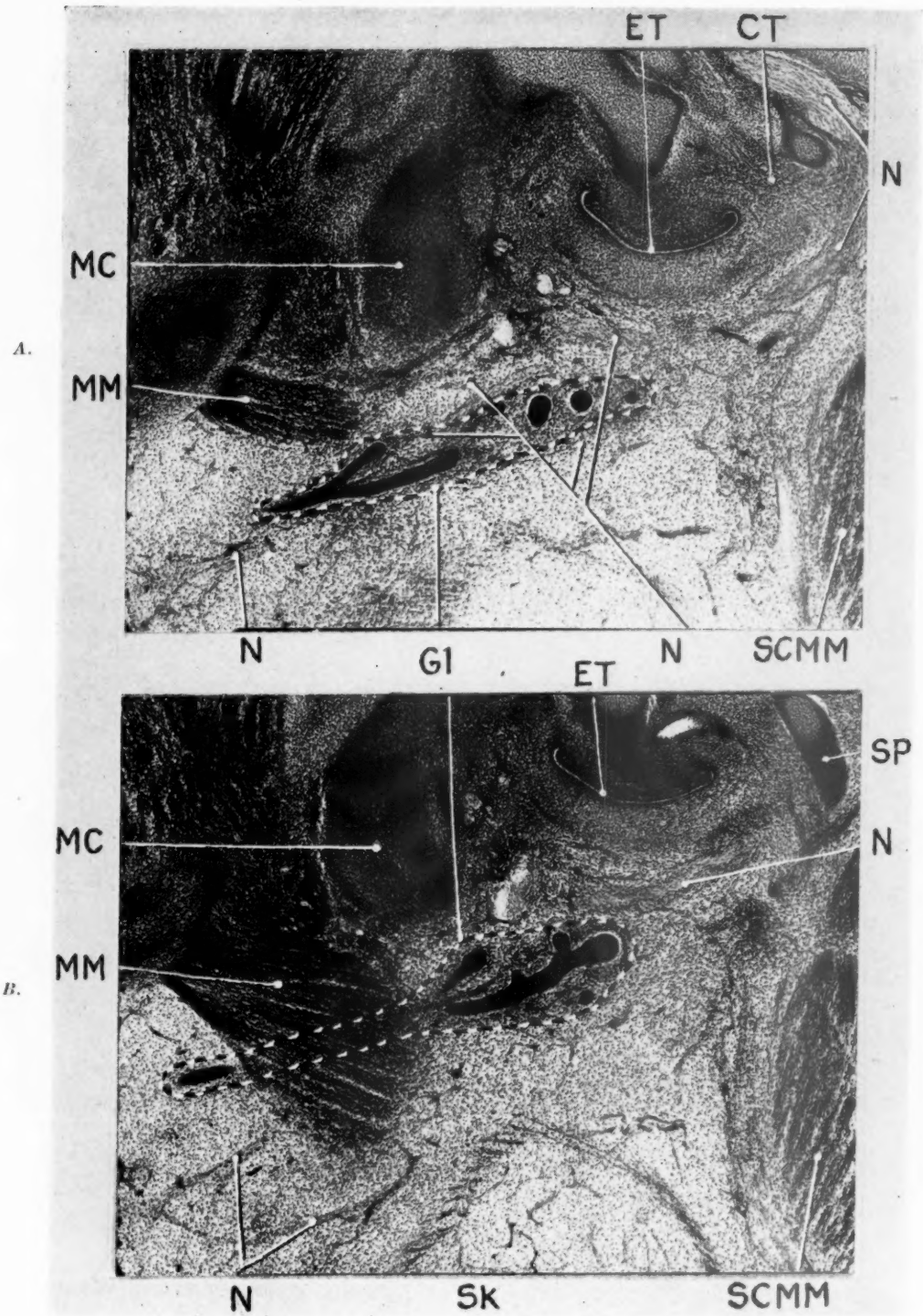
80 mm. were studied in sagittal, transverse, and coronal planes. In all cases studied the nerve pattern was apparently fully developed by the time the parotid buds reached the area of the nerve trunk. The gland primordium, which is at first a solid column of cells arising from the epithelium of the oral cavity, elongates in a dorsal direction, angling slightly caudally and laterally. It approaches the region of the facial nerve trunk, and its main axis forms an obtuse angle with the axis of the nerve. In these younger embryos the stylomastoid foramen is in a relatively much more cephalad position than

in the mature fetus, and the nerve branches approach the region of the masseter muscle and mandibular ramus in a ventrocaudal direction. The budding of this column of cells seems to begin only when the length of the column is such that the advancing tip is in the region of the primary branches of the nerve. There are many variations, but, in general, budding seems to be depressed until the main column is at some distance removed from its origin in the oral cavity. When the main column begins to bud, it appears as if only the peripheral portion of the column is involved (Fig. 5). However, in almost

A. *B.*

Fig. 4.—*A*, Anteroposterior view of a right parotid duct system showing that the large medial portion is an integral part of the whole gland. *B*, Basal view of the same specimen reveals the absence of an "isthmus" and the essentially single lobar form of the gland.

all cases there is a limited outcropping from the proximal portion of the column in a superior direction which becomes the adult accessory lobule. The budding is of a progressive type, each branch undergoing many successive divisions. There is no definite form to the pattern or direction of the enlarging gland, but it seems to progress along the lines of least resistance and to occupy whatever space is available in the region. The actively proliferating buds first occupy the area bounded roughly by the base of the skull cephalad and dorsally, Meckel's cartilage rostrally, the pharynx medially, and the



A.

B.

Fig. 5.—(Fetal length 27 mm.; sagittal sections; ×45) *A*, Extent of central portion of gland is shown. The nerve branches appear to be pushed aside by the expanding gland tissue which is outlined by the dotted line. *B*, (80 micra medial) The lower branches of the nerve are visible in the more medial section.

The following key to the labels pertains to Figs. 5 to 8. BD—bridging duct; Co—cochlea; CT—chorda tympani; EC—ear cartilage; EPtM—external pterygoid muscle; ET—eustachian tube; Gl—gland; Ma—mandible; MC—Meckel's cartilage; ME—middle ear; MM—masseter muscle; N—Nerve VII, unspecified branch; N1—Nerve VII, temporal branch; N2—Nerve VII, zygomatic branch; N3—Nerve VII, buccal branch; N4—Nerve VII, mandibular branch; N5—Nerve VII, cervical branch; SCMM—sternocleidomastoid muscle; Sk—skin; SP—styloid process.

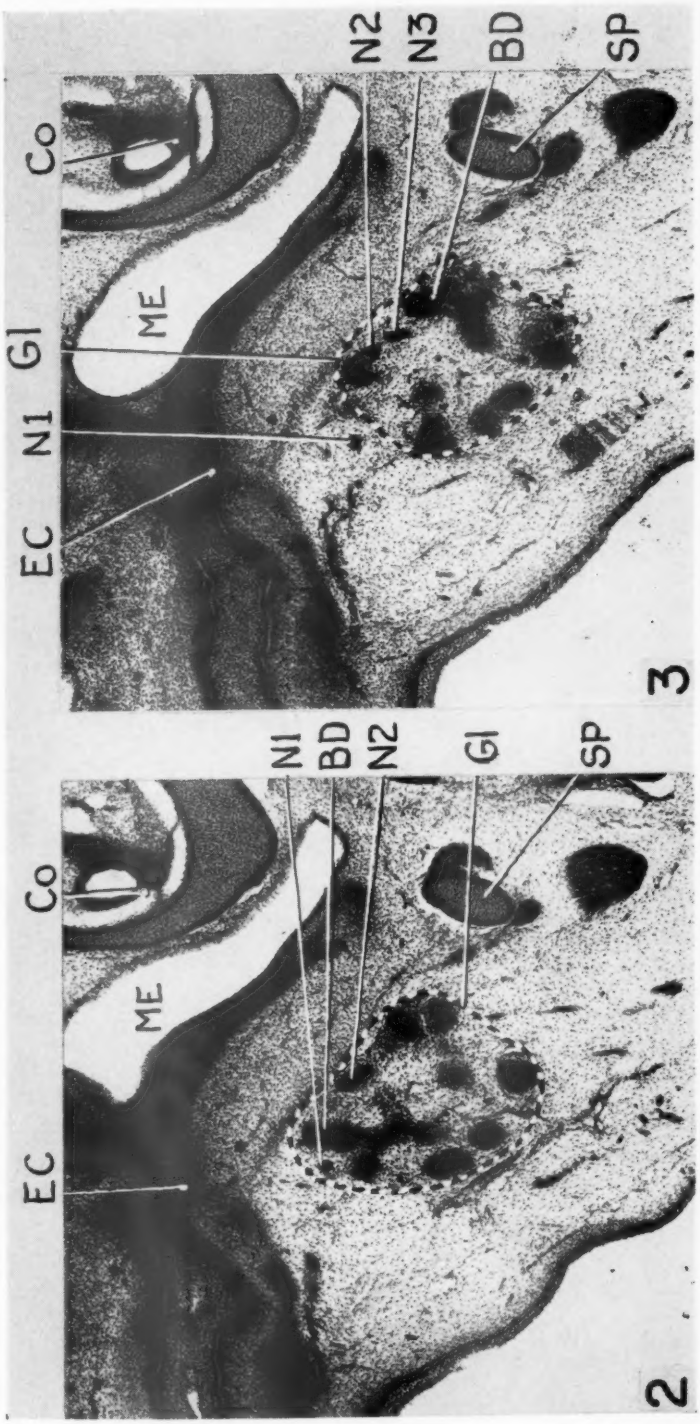
epidermis ventrally and laterally. Consequently, the main axis of growth changes its course somewhat and seems to dip medially to occupy the deeper recesses of this region. As the budding continues, the deep space now occupied by the gland fills up rapidly by encroachment of the surrounding structures into this space as they also enlarge. Because of the small size of this space and its rapid filling by the gland as well as its surrounding walls, the major budding activity then shifts to a lateral direction. This is probably due to the unyielding character of the deep structures and the relative pliability of the lateral and ventral skin covering. The proliferating gland in all cases crosses the facial nerve plane. Whether the crossing first takes place through one of the interstices of the pes anserinus or below the main trunk probably depends on the peculiarities of the nerve course and branching, the shape and configuration of the deep space and bony walls, and the individual budding pattern of the gland. It can be amply demonstrated, however, that in all cases, as the gland continues its growth, all the interstices of the branches of the nerve are filled with proliferating buds. It is evident in as early as the 10-week embryo that the bulk of most glands lies within the crotch of the main branches of the facial nerve (Fig. 5). The largest portion of gland tissue that bridges between the deep and superficial parts invariably lies in the region of the lower branches of the nerve around the cervicofacial trunk. This is apparently due to the direction of growth of the early gland which we have shown to be in a dorsocaudal direction, while the nerve arrives from a dorsocephalad direction (Fig. 8, *C*). It is also evident that the points of growth pressure of the proliferating buds, when they come in contact with the near-by nerve branches, cause a buckling and yielding of the nerves so that their course is no longer straight and direct as in the younger specimens, but rather wavy and undulating (Fig. 5). The nerves, as more buds press on them from all sides, soon appear to be rather intimately enmeshed in the gland substance (Figs. 7 and 8). McKenzie stated that the lobules seem to surround the nerve branch "just as a hand would grasp it." Also the various branches of the adult nerve do not occupy the same sagittal plane as in the early embryo. At first the mandibular and cervical branches are invariably more medial, as the splanchnocranium is at this stage quite underdeveloped in comparison to the size of the viscerocranium. Coronal sections at this stage reveal that the alignment of the nerve branches is not vertical as in the adult, but rather oblique, with the plane running from below upward and outward (Fig. 6, *D* and Fig. 6, *F*). In the adult the cervical branch seems to be consistently medial to the gland and rarely has any glandular tissue deep to it. It occupies the ventral and medial portion of the space into which the gland grows, and as a result, the continued growth of the gland takes place entirely lateral to it. The rapid growth of the face pushes this branch laterally, but it always remains deep to the tail of the gland.

From the above evidence it is possible then to construct a picture of the topographic and physiologic anatomy of the parotid gland. A study of both the embryologic and the mature forms of the gland point to its being essentially a multilobular unilobar structure with grossly irregular outlines. Its

B.

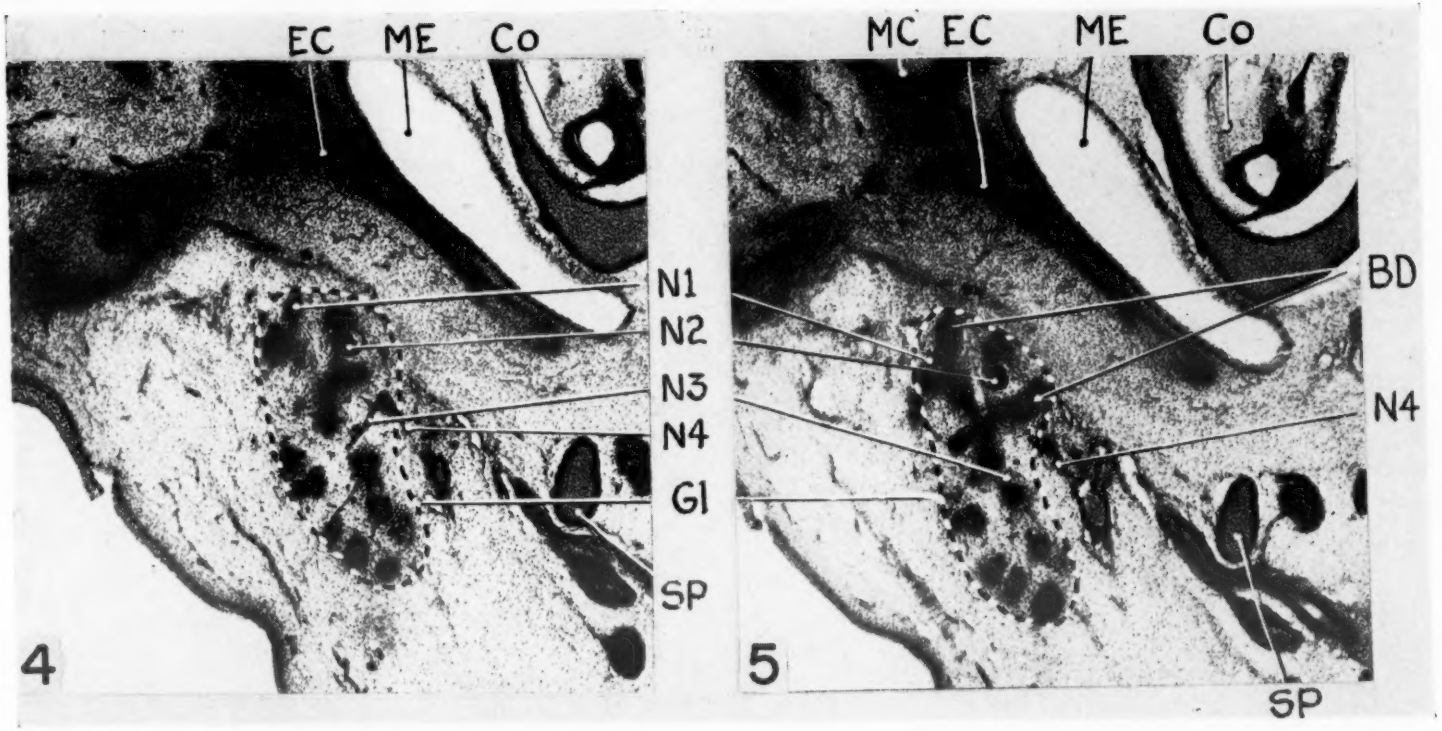
A.

Fig. 6.—(50 mm.; coronal; ×45) The numbers on the sketch (*A*) correspond to the levels of *B-H* (see numbers in lower left corners) *B*. The posterior part of the gland with the main nerve having just divided into an upper (N1) and lower (N2) trunk.



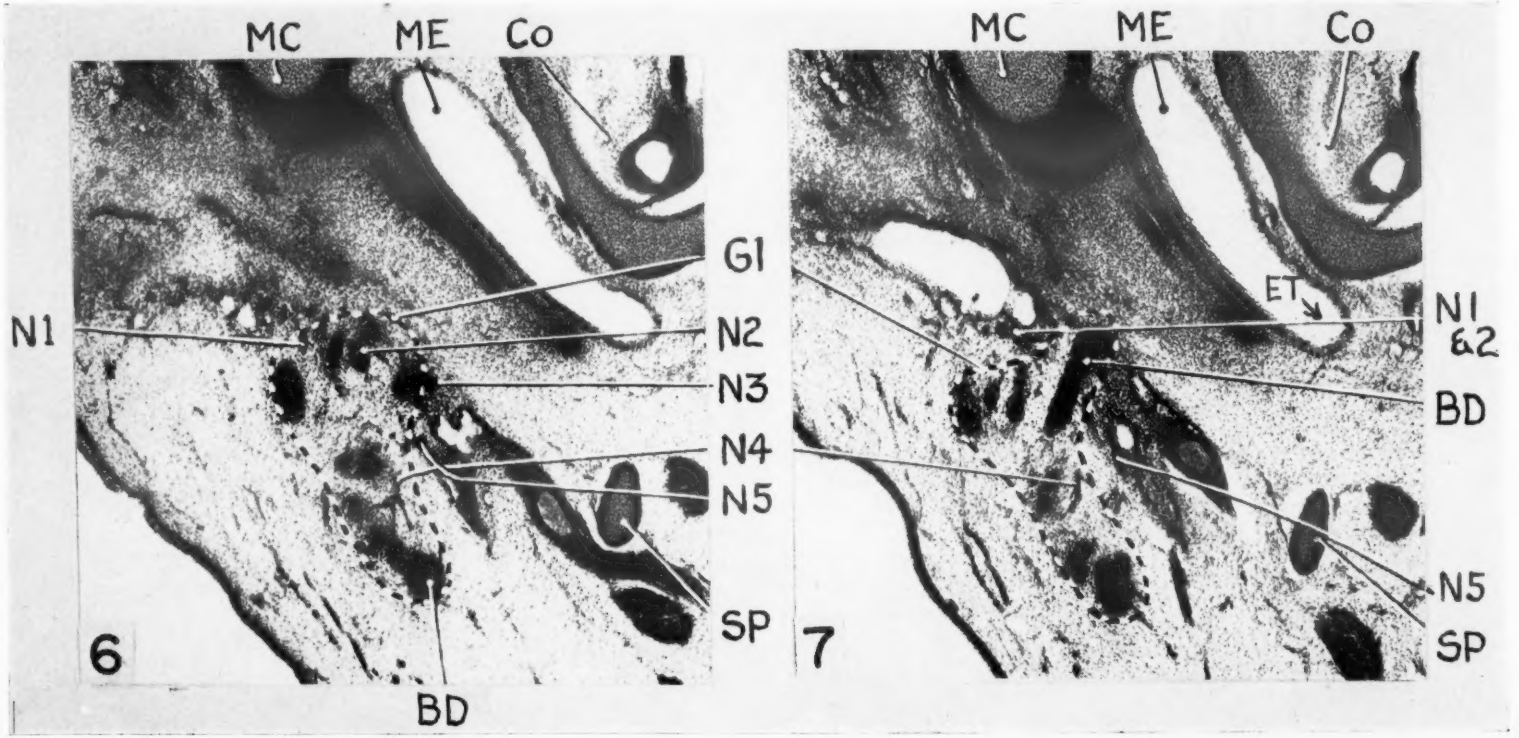
C. *D.*

Fig. 6 (Cont'd).—*C*, (520 micra anterior) Note bridging duct (BD) growing between upper trunk (N1) and lower trunk (N2). Lower trunk is about to divide. *D*, (80 micra anterior) Another bridging duct is growing below the lower trunk which has now divided into an upper branch (N2) and a lower branch (N3). Note the oblique plane occupied by the nerve branches.



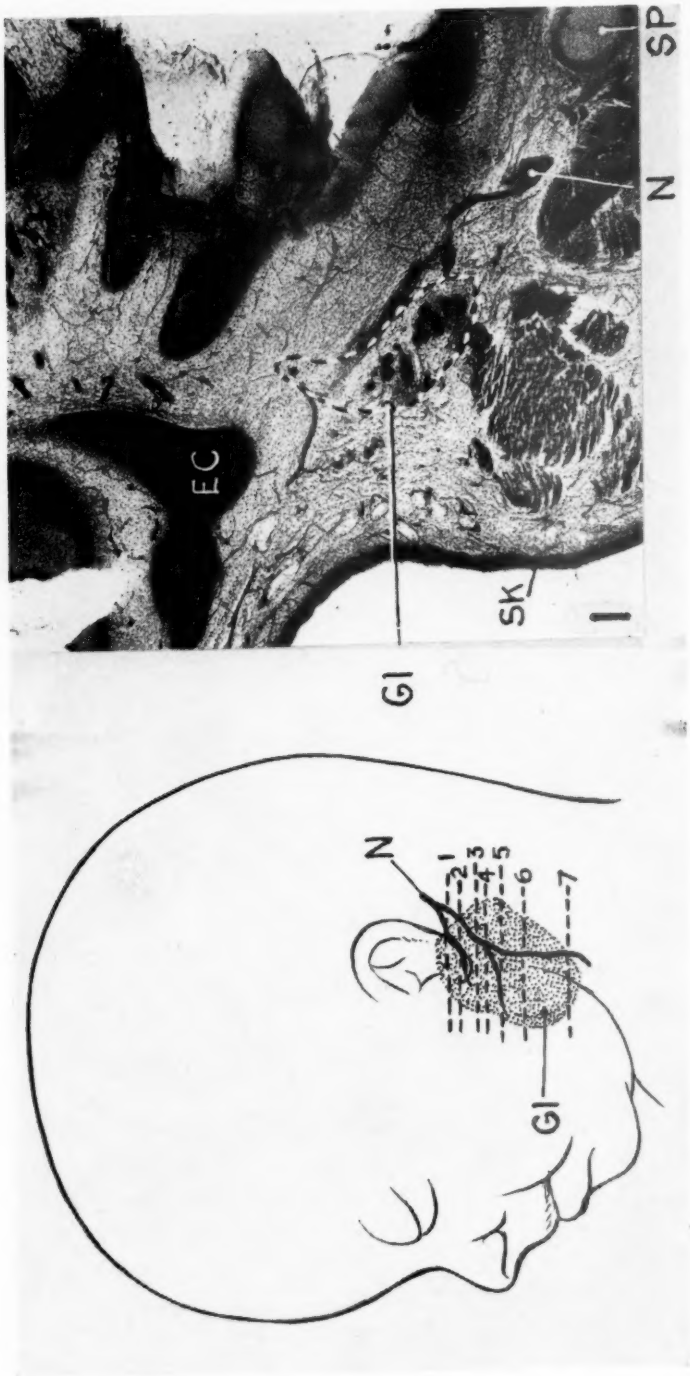
E. *F.*

Fig. 6 (Cont'd).—*E*, (160 micra anterior) Lower branch has now split into the buccal (N3) and the mandibular (N4). There is now a bridging duct growing between the zygomatic branch (N2) and the buccal branch (N3). *F*, (40 micra anterior) There is a second bridging duct (BD) pushing between the temporal branch (N1) and the zygomatic branch (N2). Note the oblique plane of the nerve branches.



G. *H.*

Fig. 6 (Cont'd).—*G*, (120 micra anterior) The mandibular branch (N4) and the cervical branch (N5) have separated. N4 is enmeshed in the gland substance and N5 continues its course medial to the gland. *H*, (120 micra anterior) The temporal branch (N1) and the zygomatic branch (N2) have merged again and below their common trunk another bridging duct (BD) is growing medially. Note that the cervical branch is still medial to the gland.

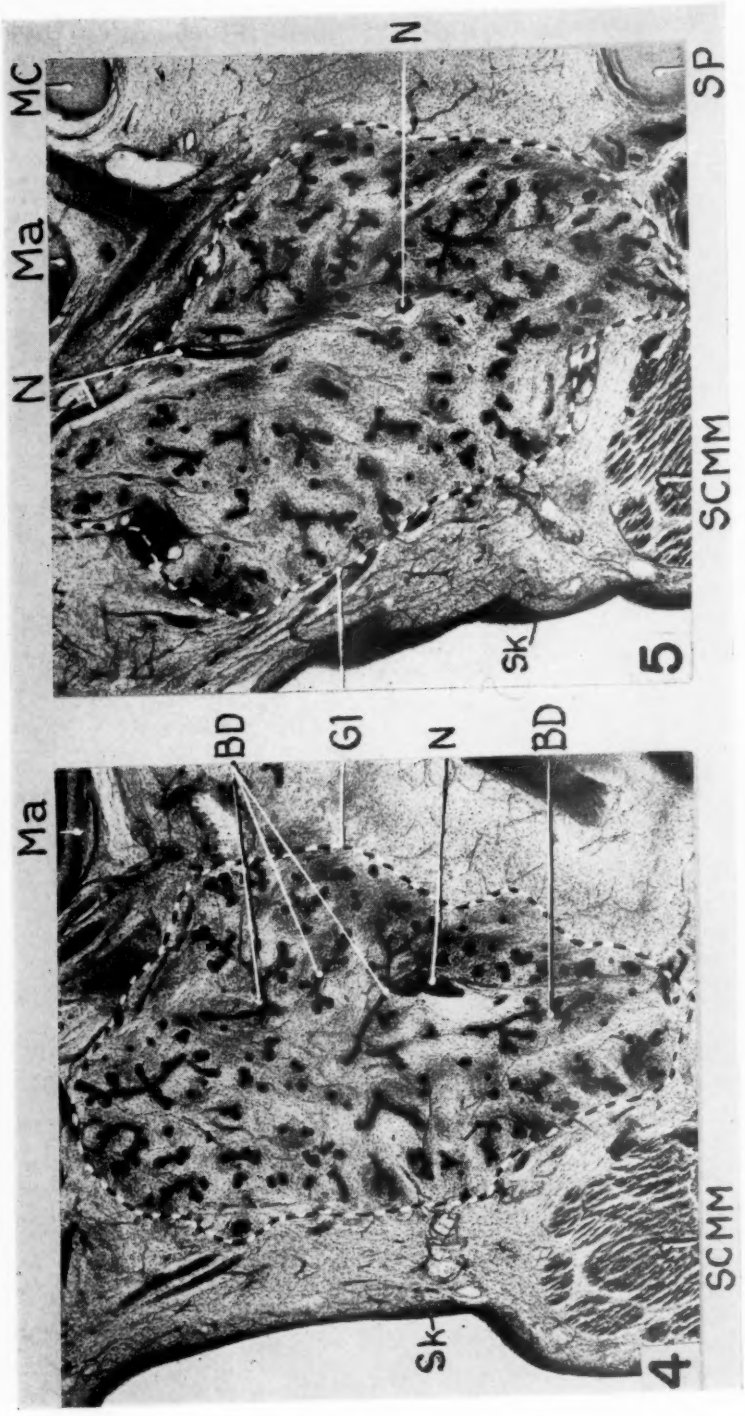


B.

A.

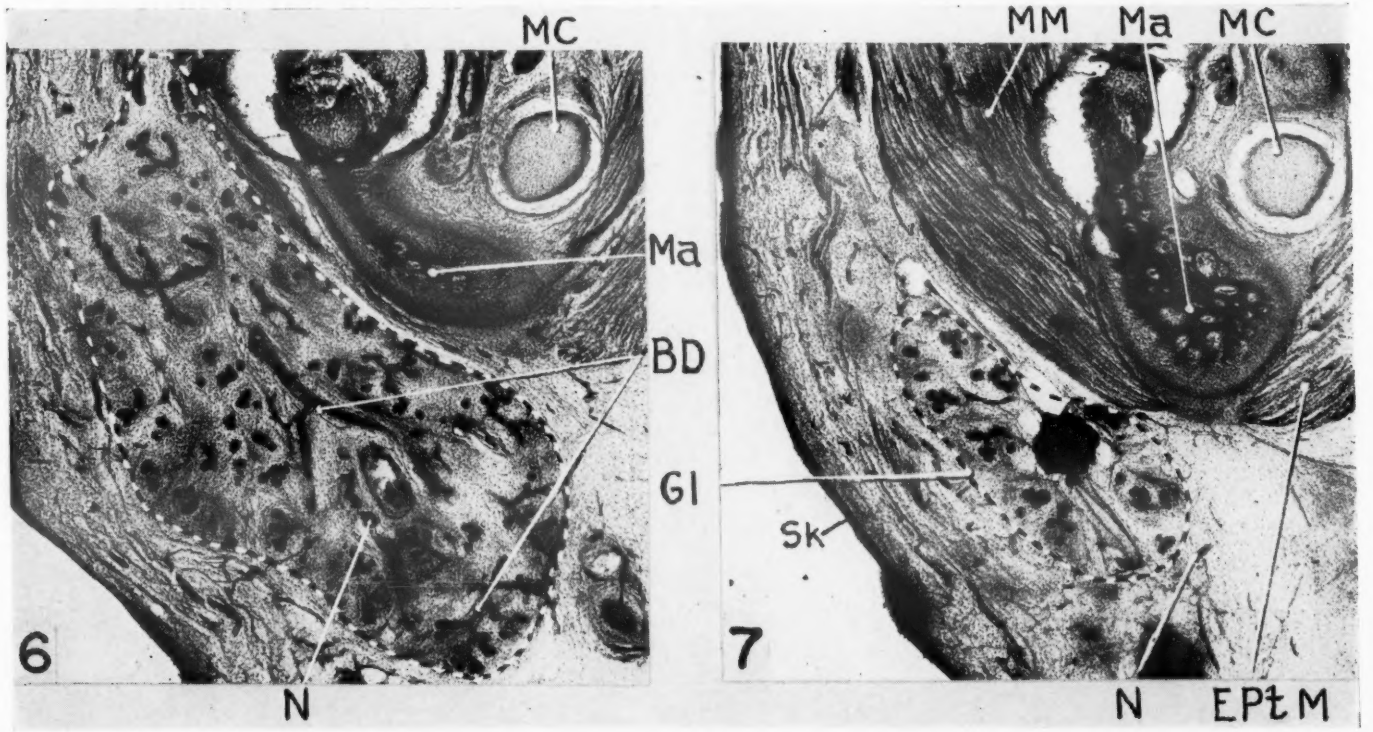
Fig. 7.—(80 mm.; transverse; ×25) The numbers on the sketch (*A*) correspond to the levels of *B-H* (see numbers in lower left corners). *B*, Most superior portion of the gland shows the nerve trunk (N) to be posterior to the gland.

Fig. 7 (Cont'd).—*C*, (200 micra caudal) Gland seems to be encircling the upper branch of the nerve. *D*, (400 micra caudal) At this level the main trunk of the nerve (N) is enveloped by the gland. Note the bridging ducts growing medially between the upper branch of the nerve (as seen in *C*) and the remaining nerve trunk.



E. *F.*

Fig. 7 (Cont'd).—*E*, (100 micra caudal) Several bridging ducts are shown, one of which is below the nerve branch, while the others are above it. *F*, (300 micra caudal) The lower nerve branch has now split, the upper part leaving the gland anteriorly and the lower part traversing the gland inferiorly.



G. *H.*

Fig. 7 (Cont'd).—*G*, (900 micra caudal) The lowest branch of the nerve is entirely surrounded by gland tissue. There are bridging ducts above and below it. The lower bridging duct is unusual in that it appears to arise from the deep portion of the gland and spread out laterally into the superficial portion. *H*, (1000 micra caudal) The lowest nerve branch is outside the gland area, and lies posteriorly and medially.

A. *B.*

Fig. 8.—(50 mm.; sagittal; ×30) *A*, This section runs through the lateral portion of the gland. Note that the middle portion of the nerve trunk is pushed medially by the expanding gland. (*C* shows the portion of the nerve absent in *A*.) *B*, (100 micra medial) Bridging ducts are seen in the distal nerve interspaces.

Fig. 8 (Cont'd).—*C*, (100 micra medial) Middle portion of main nerve trunk seen with gland tissue surrounding it. *D*, (100 micra medial) Several nerve branches are shown surrounded by gland tissue.

Fig. 8 (Cont'd).—*E*, (300 micra medial) Shows a nerve branch coursing downward and forward through the gland. *F*, (100 micra medial) The inferior branch is visible here leaving the gland area.

relationship with the facial nerve is one of intimate association. Cleavage planes in which the nerve radicles traverse the gland have been shown not to exist. The final pattern of the gland seems to be a function of the individual growth characteristics of the gland as well as of the bony and soft structures which are part of the parotid region.

It would be presumptuous to assume that these facts alone can explain the high recurrence rate of benign mixed tumors. However, the fact that the parotid gland is not made up of two lobes connected by an isthmus, around which the facial nerve branches course, should prompt surgeons to re-evaluate the approach to parotid surgery. To many, adequate excision means, for superficial lesions, a partial or total "lobectomy." This procedure is supposed to allow for a zone of normal gland tissue around the tumor and to utilize an anatomic plane for the extra margin of safety. It would appear from the foregoing material that such an operation is a misnomer, and that no reliable plane exists. Perhaps a carefully performed total parotidectomy is the only operation that fulfills the basic tenets of adequate surgical excision. The proof of this statement will probably have to await more knowledge of the biological activity of these tumors, a better system of classification, and a long follow-up of many cases.

SUMMARY

To further an understanding of the anatomy of the parotid gland and its relationship with the facial nerve, metal casts were made of the duct systems of 20 glands, and 52 embryologic specimens were studied. The resulting data revealed two main points: that the parotid gland is essentially unilobar, and that the facial nerve branches are intimately enmeshed within the gland tissue.

These anatomic facts disprove the idea held by some investigators that the parotid gland is composed of a large superficial lobe overlying the masseter muscle and angle of the mandible and a small deep lobe medial to the ascending ramus of the mandible and that these two lobes are connected by an isthmus.

It is further demonstrated that in the human embryo the facial nerve appears in the face prior to the development of the parotid gland and that the gland grows out from the primitive oral cavity across the masseter muscle and around the ascending ramus of the mandible posteriorly to lie on the pharynx. At the same time the gland grows between the branches of the nerve. There is no line of cleavage between the gland and the nerve. These anatomic relations must be borne in mind by the surgeon while operating in the region of the parotid gland and facial nerve.

Fresh cadaveric heads were furnished by the Maryland Anatomy Board through the courtesy of Dr. Eduard Uhlenhuth, Professor of Anatomy of the Medical School of the University of Maryland, and Dr. Allan Grafflin, Professor of Anatomy of Johns Hopkins Medical School.

The embryologic material was made available by the Department of Embryology, Carnegie Institution of Washington, Baltimore, Maryland, through the courtesy of Dr. George W. Corner, Director. The photography was performed by Mr. Richard D. Grill, of the Carnegie Laboratory.

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Editorials

What Is Your Program?

It seems that one person can learn surgery many times faster than another and for this reason, as well as for others, it would seem best not to have training and information too much slotted, for the individual's best process, and for the best final product. It also would seem better if acquisition of the training, and ultimately of the board certification, be sought not entirely for economic reasons.

So much has been said about, and so many ideas formulated for, training, all in search of correct answers, that the mass process sometimes overshadows the problem of the individual. This seems to have led some who seek training to make the acquiring of knowledge the chief function of someone else rather than of themselves. Endless queries and discussions of "programs" are carried on, so that the oft repeated query, "What is your program?" may call forth little enthusiam in answer. Naturally the best "program" is the goal of every applicant but searching it out often seems to become boring, as may be surmised when inquires are addressed "To Whom It May Concern."

Surgical services and hospitals exists primarily for the care and relief of patients but the idea seems to be present in some trainees' and some workers' minds that the institutions exist so they can get their training or have their job, and this gets away from the first and most important rule in surgery, the Golden Rule. It is difficult at times to have this simple precept easily accepted and yet a service can hardly exist without it. This natually includes the rule that care should be taken to do no additional harm to the patient. Politeness, an essential part of the Golden Rule, is also necessary for proper function of a surgical service down to and including the level of the operating team. It must work both ways between all concerned in the operating room, not just in one direction. Personalities creep into performance, unpleasant ones grate on others' nerves, but "patience and forbearance" and looking into the secret history of the offender, will nearly always show some reason or some suffering that "will disarm hostility" and possibly set up some chance of helping the unfortunate situation.

Learning and gaining acumen and accuracy are not objects of concrete substance, to be passed around over one patient's situation, or at the lunch table, in mass production, with an aim at a final rigid examination that will prove one's worth. These elements of knowledge are fluid, and everyone concerned needs to be constantly learning. At the time of each round, or

each procedure, or the consideration of each patient everyone concerned should learn something, whether he recognizes it as a nugget of information or not to be stored away and called forth again sometime. The chief is still always learning and he may get great help and impetus from younger men, but there is an advantage in experience that the younger men can gain from association with those who have been at it longer.

Such elements of continual study and improvement leave a place for preceptorship in surgical training in which a surgeon comes up under or along with another older more experienced man. This method of training is thought by many to be the best system, although it gets mired down in appointments and house staff arrangements at times. An example of a lack of preceptorship in spirit, if not in designation, is where it is a policy that a resident can do anything called for at any time. If this did happen to be true, then there would be no reason for the individual's being a resident since it is predicated that he already knows all there is to know.

Of greatest interest to the public is how much good can be given to the most patients, and in this respect the treatment of small lesions will do the most good. Unfortunately, however, small lesions are of little pathologic interest and are looked down on as teaching specimens and have little place of standing in board examinations. Because of the ever present desire to seem erudite in conference and to be able to meet the stiffest, most bizarre examination questions, the most time is spent on such study. So that when a small lesion is being done in an operating room, the house officers may be out reading a newspaper, and may actually miss training in elements that would be the most benefit to patients. However, when a four- or five-pound tumor is being tackled, the outcome of which possibly will be nil, the whole staff is gathered around, gleaning all possible points of procedure. This habit may become so marked that if one is truly interested in a young surgeon, he may have to have two forms of instruction, one to get him by in conference and in examinations, and the other to train him for the care of patients. Pathologic interest and instruction may become a law and a specialty itself, and may lean to pathology of a post-mortem type, rather than toward the vibrant need, and service dedication that proper surgical pathology for the living requires.

The demands of some services in conferences, seminars, and repetitious exposés of erudition may cause wonder as to what has been taught in medical school. It does not seem proper to some observers to have to repeat all elements of medical school subjects in a program of surgical training. As some colleges of today have had to quit teaching high school English as being too expensive, it would seem that medical education has a parallel in trying to fill voids of medical school knowledge in the training period. It is obvious that surgical specialties require long periods of training and that such would be of little value in medical school. But while in medical school it might be better for would-be surgeons to concentrate most on medicine, if such a concept could be held by medical instructors.

The above are just suggestions, versus the situation in which the aspirant writes for dozens of "programs", signs up for one, and then wants a standard form of instruction guaranteed to get him through the board. It sometimes seems that packing the information in through a trephine opening, layer by layer, might be easiest; and some have assumed that information might seep in through the chest wall if an open text were balanced there during an afternoon nap.

Economics plays a great role in training, and in the modern concept of raising families while in training. Much can be said for this latter situation in that nonmedical college classmates are found to be many years ahead of medical trainees in position and income. A difficulty exists, however, that there practically isn't such a thing as a full-time "house" officer or resident any longer. They are practically all established outside the hospital and tend to have hours on and off duty as in a service or governmental setup. Even house staff quarters are a thing of the past in many places, the rooms being little more than transient rest places, hardly recognizable as living quarters for someone assigned to a hospital.

The specialty boards started out on a voluntary effort basis for some men to submit to advance examinations and investigations after prescribed years of training, to be given a certificate of merit as to their effort and their possible proficiency. This idea was soon turned into an economic one, however, whereby hospital appointments were based on it, governmental service pay was influenced by it, and the voluntary effort to gain and to be able to display merit fell short of its first impetus. The information necessary for these attainments becomes slotted, and a rigid state develops that may be not as desirable as a free enterprise system of trying to be proficient in one's own right and by one's own work and effort.

For further work in surgical specialties the added years for further board certification bring up men advanced in years who are over their best value as assistants in the operating room, who often are burdened down with search for the best answers to board examinations and to questions in conferences, and nearly always burdened by still further search for the most advantageous appointments.

Whereas, it is a most commendable situation to see the chief or older surgeon assisting a resident or house officer, it is possible for the observant instructors to know even better than the trainee when he is ready to go ahead on his own. One element that the resident may sadly lack in his training is the ability to get into the spirit of service to the patient at hand that the chief is operating on, and to see to it that the flow of operating room service and his own help and interest with the patient are to the greatest benefit for the patient on the operating table in front of him. Such spirit is far more important to the patient and to medicine as a whole, rather than an argumentative, quizzing period during the operation of erudition, and feeling belated if

some august advance in one's knowledge and skill has not resulted from the procedure. Surgical services are for beneficial service to individual patients.

If there could be a sliding scale of coming into a productive position by continued work on a recognized service that had proved itself worthy, perhaps some of the prescribed formula could be taken less seriously and a better final product be found at hand. A decent productive service that has cared for patients successfully (which is the professed object of all instruction and examination) might be in a position to say that certain of their trainees are ready for places of responsibility, and may be recognized as being well trained.

In the United Kingdom fellowship examinations have been carried to a point where one may be so designated with very little operative experience. In this country fellowship in the College requires more evidence of successful technical skill. We do seem lacking some classicism of the United Kingdom, as they seem to lack some of the pactical application of our system. If the two areas could blend, classicism and practicality, a little better, both might have a better product. Slotted information, as the final province of all at equal level, with a certificate that proves it, is not a goal that suggests capability of going ahead of the crowd.

"What is your program?" is a good question for anyone going into a chosen field. But services should be known by their works and their products and not selected by a printed form, or promise of stipend. The hard questions and the influence of the boards in ferreting them out have, can, and will produce top-flight surgeons. We should not lose any strides for proficiency we have made. These elements require that the individual make the effort and prove his progress. Such individual effort must stimulate the instructor as well as the instructor's stimulating the student. Becoming able to give patients, who seek relief, what we would wish for them, or what they deserve must start primarily with the individual's own determination. It can't be by someone else's deciding at every turn just what program is needed for a whole group of trainees at each moment of the day.

Programs must be good or there wouldn't be so many of them, or so many people and governments and institutions wouldn't turn to them, and constantly change them and try out entirely new ones. But at least they do not make uniform standard final success for the individual, no matter how glowing the slotted erudition may sound in conference or on paper. Instead they may be like Tristram Shandy's father, Walter, who, in his interminable speeches, was said to have been carried away by his own eloquence, but was every minute a dupe to it.

Everyone wishes for the best possible outcome for his career. There are few shortcuts, and one may do best by mapping and overseeing his own "program."

—*James Barrett Brown.*

The Epiphenomena of Total Right Hepatic Lobectomy

The entire right lobe of the liver is being resected with increasing frequency for such indications as primary malignant tumors (hepatoma, cholangiocarcinoma, and somatic sarcoma), unilobar metastases, cancer of the gall bladder, and occasional benign tumors. Surgeons have been unreasonably delinquent in attempting major surgical resections of this viscus, the largest organ in the body. The right lobe consists of 80 per cent of the weight of the human liver, yet it now is feasible and relatively safe to perform total right hepatic lobectomy by the controlled hemostatic procedure of preliminary ligation and severance of the right hepatic duct, the right hepatic artery, and the right branch of the portal vein prior to transection of the interlobar septum. In earlier years we were intimidated by our concept of the liver as a human vascular sponge with an intricate triple circulation, viz., a high pressure hepatic arterial supply accounting for 40 per cent of the afferent blood, a low pressure portal venous system furnishing 60 per cent of the afferent blood, and the intrinsic and extrinsic biliary system. To the fear of hemorrhage was added the supposed hazard of hepatic insufficiency, because most of us had been told that the liver possessed at least 70 different functions, many of which were vital.

We surgeons have failed to appreciate that a residual 20 per cent of the liver substance is enough for the maintenance of life if the subject is an otherwise normally functioning organism. Our colleagues in internal medicine and pathology, for example, have long been aware that the tremendous parenchymal loss which attends acute yellow atrophy and the toxic necroses may exceed the 75 to 80 per cent we conventionally remove by right lobectomy, yet once destruction ends and regeneration begins, the human liver may grow as rapidly as 50 Gm. or more daily. The Grecian mythologists were aware, seemingly, of this irresistable urge of the liver to regenerate itself as recorded in the legend of Prometheus. In compassion for the frailty of human beings he was said to have stolen a bit of fire from the sun and given it to mortals. According to the story, Jove became angered at his presumption and chained Prometheus on the Mountain top where the vultures ate away his liver during the day, but it completely grew back during the night. According to the Babylonian Talmud Tractate, Mishnah Hullim, III, if most of the liver of an animal is gone but a part of it at least equal to an olive in bulk remains, the animal is kosher, provided the death of the animal be the result of slaughtering. Therefore the passage indicates that although most of the liver is gone, the animal can continue to live under this handicap.

In some humans frequent repetition of liver function tests may show an immediate improvement during the postoperative period, the best testimony to the adequacy of the minute left lobe. If the major portion of the right lobe is replaced by neoplasm, the trend toward resumption of normal liver function may be manifest on the first postoperative day. Explanation of this paradox lies in the fact that portal venous blood reaching the defective right lobe may not find sufficient normal parenchyma to complete its destined func-

tion, but the abrupt shunting of all portal blood to the tiny left lobe at the climactic ligation of the right branch of the portal vein, permits the residual remnant to exert its amazing functional capacity on the entire portal blood stream which it is normally capable of doing with great efficiency. Postoperative evidence of clinical and chemical jaundice, although frightening to the tyro, is no cause for alarm because it is not due to faulty ligation of the left hepatic ducts and it is unlikely to be a coincident viral hepatitis but rather a transient phenomenon due to extrinsic pressure on the intrahepatic bile ducts by the intense portal venous congestion within a liver slow to expand. Fibrinogen production is usually unimpaired unless inhibited by excessive blood transfusions.

In no other gastrointestinal operation is the need for immediate alimentation so imperative. Maintenance of a positive nitrogen balance by the intravenous exhibition of amino acids is not the answer. The impulse for liver regeneration in the left lobe is initiated at the very moment the right lobe is excised and the body metabolism at this critical time should be in readiness for this emergency. Preoperative starvation is contraindicated, and a high protein preparatory diet is the best possible preparation. Good old-fashioned protein by mouth to supply the portal system and the liver remnant with at least the partially converted nutrient elements and an adequate carbohydrate intake should be given postoperatively as soon as feasible. The time elapsing before the administration and tolerance of proper feeding may determine the survival of the patient. Total right hepatic lobectomy usually causes some degree of hypoproteinemia (hypoalbuminemia and hypoglobulinemia) but the rapidly regenerative left hepatic lobe in the presence of an adequate protein intake soon elevates this deficiency to the normal standard.

The increased bulk of the left lobe is not due simply to vascular engorgement and edema but rather to a true proliferation of new liver tissue. Once the immediate adaptation to the increased blood flow has occurred, chemical analysis of aliquot parts of the regenerated, as compared with the normal, liver show identical values for lipid, nitrogen, and water content. Furthermore, the nuclear counts of homogenized liver tissue reveal a normal level in the rat within three days, increased above the normal by the fifth postoperative day, and then resumption of normal values. Similar studies of the residual dog liver confirm the tenet that the increased liver substance is due to a true regenerative hyperplasia of parenchyma and not a vascular artefact.

The rapidity and completeness of liver regeneration after subtotal hepatectomy appear to be inversely proportional to the size of the animal, e.g., as in rats, dogs, and humans. In rats the liver has completely regenerated within 12 to 18 days after major lobectomies. In dogs the remnant of residual liver after 75 per cent hepatectomy has grown to the original proportion within eight weeks after the operation. In the human the process of regenerative hyperplasia is not so easily followed because of the infrequency of "second-look" observations and measurements. In one human, two years after total right hepatic lobectomy we found on exploratory laparotomy that the left lobe had expanded to fill the

entire cupola of the diaphragm, assuming final dimensions greater than the original liver. The larger the proportion of the liver excised, the greater is the rapidity and the more complete the regeneration experienced; for example, in the experimental ablation of 55 per cent and 70 per cent of the liver in the rat. Within the limits of survival it would seem proper to make the general statement that the stimulus to hepatic regeneration is directly proportionate to the percentage of liver excised. The regenerative hyperplasia proceeds only from the residual lobe which tends to enlarge in a rounded spherical form and not to assume the contours peculiar to the excised lobes. Thus, in the human the regenerated liver can usually be palpated as a rounded, smooth, spherical mass occupying the epigastrium and sometimes confused with metastatic cancer in the residual lobe.

The clinical and experimental surgeon must conclude that the factors initiating and maintaining liver regeneration are not solely the impulses of wound repair, but are varied and in part unfathomable at the present writing. The nutritive element and the inhibition of bacterial growth by the routine employment of antibiotics are of influence but there also must be the ill-defined stimulus in response to a functional demand. In two human patients who were unexplainably almost moribund after total right hepatic lobectomy, the administration of cortisone brought about immediate and successful recoveries. In subsequent experiments, cortisone-stimulated rats showed a definite acceleration of liver regeneration as compared with controls. In parabiotic rats, subtotal hepatectomy in one resulted in liver enlargement within its nonresected partner, a phenomenon which we interpreted as proof that some humoral factor was present.

The influence of the portal venous pressure on the start and completion of liver regeneration should not be discounted. Experimental hepatic regeneration is intimately linked with the quantity of portal blood traversing the organ. In fact, after total right hepatic lobectomy and the consequent ligation of the right branch of the portal vein, portal hypertension in the remaining left lobe due to complete shunting of the portal stream is not only inevitable but highly beneficial in promoting rapid regenerative hyperplasia. Per contra, partial hepatectomy and diversion or decrease of the portal blood flow by means of an Eck fistula causes inhibition of liver regeneration in animals. The portal venous pressure in humans and dogs increases with the amount of liver removed. The rapidity of regenerative hyperplasia of the residual liver tissue, other conditions being on a par, is directly proportionate to the degree of portal hypertension. The portal venous pressure returns to normal when the liver is anatomically and physiologically restored. Finally, major hepatectomy and arterialization of the portal venous system magnify the portal hypertension still more and pari passu hasten the regenerative hyperplasia in the liver remnant. It is conceivable that in instances of deficiency of the residual liver or impairment of its vascular supply, arterialization of the portal venous system may find clinical application in the human patient.

Parenthetically, the subject of liver tumors and their treatment is so timely that the International Union Against Cancer, representing 53 participating nations, has appointed a committee of 30 physicians representing all related disciplines to convene in August, 1956, in Leopoldville, the Belgian Congo, to study liver cancer in the Bantu natives, among whom the disease causes 40 to 60 per cent of all cancer deaths.

—*George T. Pack, and*
Abdol H. Islami.

Appraisal of Progress in Surgical Therapy

CONDUCTED BY WARREN H. COLE, M.D.
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INJURIES OF THE SPLEEN

A REPORT OF 102 PATIENTS AND A REVIEW OF THE LITERATURE

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THE literature of the past two decades contains many references to injuries of the spleen. Most of the reports have discussed only injuries inflicted by blunt trauma; others have emphasized its sequela, the phenomenon of delayed rupture.

Because of the limited scope of most of the earlier surveys, the opportunity to study, over a period of ten years, the results of therapy of 102 consecutive patients with splenic injury in a teaching center appeared worth while.

The history of surgery of the spleen can be traced back many centuries when splenectomy was performed in an effort to "improve the wind" of runners.[123] Pliny (A.D. 23-79) made the observation that "sometimes it is a peculiar hindrance to runners, so that they burn it (the spleen) away from those runners who are uncommoded by it." It is of interest that one of the more unusual methods of assassination employed by the ancient Chinese was that of inflicting a blow over the area of an enlarged spleen.[28] The Medical and Surgical History of the Civil War,[113] published in 1876, recorded 30 battle casualties with penetrating wounds of the spleen. The author tabulated from the world's literature the histories of 26 patients having previously (1549-1869) undergone partial or total splenectomy for disease or trauma.[2, 33, 81, 104, 161] Of these, 17 were performed for trauma. Mention is made in one old textbook[133] indicating that there was a sect of surgeons which acquired notoriety about 1700 because of their operations for removing the spleen.

The splenic trauma which came to the attention of physicians during these times was often of the penetrating type. Although the survivors represented only a small minority of the total number injured, the observations of the clinicians of that day remain of interest. Protrusion of an injured organ was regarded "rather as a favorable than as an untoward occurrence."[66] Such a protruding spleen would often stop bleeding due to its compression by the edges of the wound. It was thought that such a wounded, protruding organ should be reinserted into the abdomen unless "it appears that the wound is large, and disposed to bleed much, for, in such a case, it would be much better to let the part remain in its impacted situation than to restore it to the abdominal cavity, thereby favoring profuse effusion from the divided and now unsupported vessels." In those patients in whom the

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spleen had protruded several days when first seen, the treatment was not to attempt restoration of the projecting portion, "lest it should mortify, or lead to dangerous hemorrhages, but to excise it on a level with the surrounding tissue."

While splenic injuries per se were probably not often recognized before the last century, physicians of that time were indeed aware of the consequences of abdominal injury. In a text published in 1881,[77] it was stated that sudden shock from a blow to the abdomen might occur without any external evidence of etiology. Although such shock due to hemorrhage was considered usually fatal, the more favorable conditions were those in which injury was followed by peritonitis. The recommended therapy consisted of application of leeches to the abdomen, followed by large hot fomentations of moist flannels, large doses of opium, and avoidance of purgatives.

In the late Eighteenth Century, surgeons considered the spleen as vulnerable an organ as the heart because of its vascularity. "A wound of the spleen, liver, or vena cava is as deadly as a wound of the heart, so full are they of blood."[22] Several authors were cited who had observed proved splenic injuries which were later found to have healed, thereby introducing the concept that not all splenic injuries were fatal.[4, 20] Such a patient was described by Behan[20] in 1865. The individual died of Bright's disease four years after receiving a gunshot wound of the colon. At autopsy a fragment of the bullet was found in the spleen.

Berger,[23] in 1902, expressed the gravity of splenic injury in his day by stating that, if untreated, 50 per cent of the patients would die within the first hour after injury, and that 95 per cent would die within the first twenty-four hours. Baudet,[19] in the same year, emphasized an interval of quiescence that occasionally followed splenic trauma in which, for reasons to be described later, hemorrhage ceased, only to resume some time beyond forty-eight hours from the time of injury. This has since been known as the "latent period of Baudet." Although this variant of secondary or delayed hemorrhage was recognized as early as 1876,[77, 113] McIndoe,[107] in 1932, collected the first series of 45 such patients and described the syndrome in detail. Subsequently, frequent articles have appeared dealing with the general subject of splenic injury, the less common phenomenon of delayed splenic rupture, the rare phenomenon of splenosis, and the questionable phenomenon of spontaneous rupture.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

The spleen's capsule is a thin fibrous layer surrounding a friable parenchymal interior. It is capable of involuntary contraction in response to the autonomic nerve supply mediated through the celiac plexus. This capsule contracts during periods of asphyxia, hemorrhage, exercise, and emotional excitement.[165] Barcroft and associates[16] found the spleen to contract and expand at intervals of approximately thirty to sixty seconds. Only minor blood pressure changes were noted with these contractions. Hargis and Masson[71] made, in dogs, a direct plethysmographic study of the spleen through a celluloid window in the abdominal wall. They estimated that one-sixth of the blood volume could be stored in the spleen and they were able to observe vigorous contractions of the spleen during hemorrhage, narcosis, and muscular activity. They concluded that the normal dynamic activity of the spleen did not increase the susceptibility of this organ to rupture.

The splenic artery is the largest branch of the celiac axis. It is not well known that its course is as variable as that of the cystic artery.[114] Perhaps such anatomic variations are responsible for at least some of the variations in the pathologic changes occurring in splenic rupture, for hilar tears are not rare.

Traumatic diaphragmatic hernias occur less frequently on the right than the left side[3, 40, 72, 73, 79, 132] because of the protection offered by the liver to the right leaf. Adams and Musselman,[3] in 1954, presented five patients with rupture of the left diaphragm associated with damage to the left kidney or spleen, or both. They stressed the importance of careful evaluation of all three of these structures in any severe injury to the left upper quadrant or lower left chest because of their anatomic proximity.

PATIENTS

Splenic injury in children is relatively uncommon. This is probably due in part to the fact that they are less subject than are adults to the most severe forms of trauma. Scott and Bowman[144] reported splenic injuries in only seven children seen over a period of fifteen years in a large children's hospital. Prior to that time, a review in 1939 contained reports of only ninety children with this injury.[5] In successive studies from the Harlem Hospital, Wright and Prigot[169] found that 30 per cent of their series, and Connors[43] found that 36 per cent of his series, occurred in the 0-10 year age group, but both studies represented primarily experiences with blunt trauma. Automobile and other similar accidents accounted for almost the entire group. Mazel[112] suggested that rupture from blunt trauma occurs more easily in children because the flexibility of their rib cage allows transmission of blows directly to the spleen. In our series, five children in one healthy family were involved in an automobile accident on the morning of April 8, 1955. They were all admitted to the emergency room of the Jefferson Davis Hospital about mid-morning of that day, each with a tentative diagnosis of splenic rupture. Following a period of observation, three of the children were explored and the diagnosis confirmed.

Johnson[85] found the peak incidence to be in the third decade. Roettig and his associates[135] stated that 81 per cent of their patients were less than 40 years of age. Our figures (Table I) would support the latter authors; the peak incidence being in the third and fourth decades. While the number of pediatric and geriatric patients is small, these two age groups carry the highest mortality; a finding which has been observed in hepatic injuries.[115]

TABLE I. AGE VS. MORTALITY

AGE	NUMBER OF PATIENTS	NUMBER OF DEATHS	MORTALITY (PER CENT)
0-9	6	2	33
10-19	11	2	18
20-29	31	5	16
30-39	22	4	18
40-49	13	4	31
50-59	12	3	25
60-69	3	2	67
70 & over	4	3	75
Total	102	25	24

The incidence, by race and sex, is probably of little importance in evaluating this problem. Of the 102 patients, there were 85 males and 17 females, or a ratio of 5 to 1. The mortality was identical in the two sexes.

INJURIES

Among general admissions to hospitals the incidence of splenic rupture is relatively uncommon, being recorded as a little over 0.1 per cent.[135, 169] The incidence is quite high, however, if one limits the study to patients with abdominal injuries. Thus, among abdominal injuries the incidence of splenic injury has been reported between 30-48 per cent.[30, 36, 112, 169, 170] By comparison, in Wright's group of 63 patients with blunt abdominal injuries, the spleen was involved in 47.6 per cent, the liver in 28.6 per cent, the intestinal tract in 18.5 per cent, mesentery in 4.7 per cent, and the pancreas in 1.6 per cent.

The high incidence of splenic trauma among patients with abdominal injuries in civilian life reflects the frequency of blunt trauma, especially that caused by automobile accidents. Of a total of 53 patients with blunt trauma in the current series, 34 had injuries which were incurred in an automobile accident, either as a passenger or a pedestrian (Table II).

TABLE II. MODE OF INJURY

MODE OF INJURY	NUMBER OF PATIENTS	PERCENTAGE OF TOTAL GROUP
Penetrating		
Stab	21	21
Bullet	27	26
Shotgun	1	1
Total	49	48
Blunt		
Auto accident	34	33
Fall	8	8
Blows	6	6
Bicycle accident	1	1
Uncertain	4	4
Total	53	52

Military campaigns reveal a far different incidence of splenic trauma. Among a group of 3,546 patients with abdominal wounds in the American Expeditionary Forces of World War I, there were but 49 patients with splenic injuries, an incidence of 1.3 per cent.[101] The estimated frequency of splenic injury among British troops in the early days of World War II was 5.6 per cent of the casualties with abdominal injuries.[12] In the Battle of El Alamein in World War II, the incidence of splenic injuries among the British troops with abdominal injuries was 3.3 per cent,[58] among American troops in the Western Desert 5.1 per cent,[120] and in the 2nd Auxiliary Surgical Group, between 1944 and 1945, 10.8 per cent.[128] In Korea, among 636 casualties with abdominal injuries reported by the Surgical Research Team in Korea, the incidence of splenic injury was 8.5 per cent.[141] It is of interest to note that blast injuries traumatized the spleen more than any other organ.[62]

In most patients with splenic rupture, a history of blunt or penetrating injury to the chest or abdomen can be elicited. In 1932, McIndoe[107] established the criteria for immediate and delayed hemorrhage as occurring within and after forty-eight hours from the time of injury, respectively. This has since become axiomatic. Most civilian studies demonstrate blunt trauma to be the predominant type of injury. The incidence of delayed hemorrhage has been stated to be about 14 per cent,[156, 170] although more recent series indicate a higher incidence. Johnson,[85] in 1954, reported 30 patients with delayed hemorrhage from a group of 85 patients, an incidence of 35 per cent. Eleven patients among our total group of 102 patients (11 per cent) presented the syndrome of delayed hemorrhage. The 53 patients with blunt trauma included 10 of the patients with delayed hemorrhage, an incidence in this group of 19 per cent.

In Table III the mode of injury in immediate and delayed rupture in blunt trauma is compared as to incidence. In each group, injury from auto accident is the most frequent mode of injury.

TABLE III. IMMEDIATE VS. DELAYED RUPTURE IN BLUNT TRAUMA (53 PATIENTS)

	IMMEDIATE RUPTURE		DELAYED RUPTURE	
MODE OF INJURY	NUMBER OF PATIENTS	PERCENTAGE OF IMMEDIATE GROUP	NUMBER OF PATIENTS	PERCENTAGE OF DELAYED GROUP
Auto accidents	32	74	3	30
Blows	5	12	1	11
Falls	6	14	2	20
Unknown	--	--	4	40
Total	43	100	10	100

Four of our patients with delayed rupture initially gave no history of trauma, although, in each instance, careful postoperative questioning established an approximate date of injury. Previously, these patients might have been considered to have had spontaneous splenic ruptures. In each instance, however, there apparently was a traumatic factor that was directly responsible for the original hemorrhage.

TABLE IV. MODE OF INJURY VS. MORTALITY

TYPE OF INJURY	NUMBER OF PATIENTS	NUMBER OF DEATHS	MORTALITY (PER CENT)
Penetrating			
Stab	21	0	0
Bullet	27	12	44
Shotgun	1	0	--
Total	49	12	24
Blunt			
Auto accident	34	9	26
Falls	8	3	37
Blows	6	1	17
Hit by bicycle	1	0	--
Unknown	4	0	--
Total	53	13	24
Total series	102	25	24.5

The mode of injury reflected itself dramatically in the mortality rates: no deaths resulting among the 21 patients with stab wounds, 12 (44 per cent) of the 27 patients with bullet wounds dying (Table IV). The mortality of penetrating versus blunt trauma was identical, 24 per cent.

There was a dramatic difference in the mortality between immediate rupture (27 per cent) and delayed rupture (1 per cent) (Table V).

TABLE V. COMPARATIVE MORTALITY IN DELAYED VS. IMMEDIATE RUPTURE

	NUMBER OF PATIENTS	NUMBER OF DEATHS	MORTALITY (PER CENT)
Immediate rupture	91	25	27
Delayed rupture	11	0	0
Total	102	25	24

ASSOCIATED INJURIES

Associated injuries in patients with splenic trauma are frequent. The incidence of the associated injuries from blunt trauma has repeatedly been shown to be fairly constant (Table VI). As might have been anticipated, fractured ribs constitute the most frequent injury, with other fractures being second. Injury to other abdominal organs is much less frequent. In the 53 patients with blunt trauma included in the current series, 34 per cent had other fractures, and 19 per cent had major head injuries (Table VII).

TABLE VI. ASSOCIATED INJURIES; BLUNT TRAUMA

ASSOCIATED INJURY	30 PATIENTS*		22 PATIENTS†	
	NUMBER	PER CENT	NUMBER	PER CENT
Fractured ribs	10	33	5	23
Hemothorax; pneumothorax	4	13	3	14
Fracture (except ribs and skull)	8	27	3	14
Head injury	3	10	-	0
Ruptured kidney	6	20	2	9
Ruptured liver	3	10	2	9
Miscellaneous	2	7	2	9

*Wright, L. T. and Prigot, Aaron. See ref. 169.
†Roettig, L. C., Nusbaum, W. D., and Curtis, G. M. See ref. 135.

TABLE VII. INCIDENCE OF ASSOCIATED INJURIES

ORGAN	TOTAL GROUP (102 PATIENTS)		PENETRATING INJURY (49 PATIENTS)		BLUNT INJURY (53 PATIENTS)	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Chest	32	31	14	29	18	34
Diaphragm	27	26	24	49	3	6
Stomach	24	24	23	47	1	2
Small bowel	11	11	9	18	2	4
Colon	14	14	13	27	1	2
Kidney	13	13	12	24	1	2
Liver	9	9	8	16	1	2
Pancreas	4	4	4	8	0	0
Fracture (excluding ribs and skull)	13	13	0	0	13	24
Head	10	10	0	0	10	19
Inferior vena cava	3	3	3	6	0	0
Heart	3	3	2	4	1	2
Miscellaneous	3	3	2	4	1	2

The 49 patients with penetrating injuries, constituting 48 per cent of the total group of this series, confirmed the impression that associated multivisceral injuries are much more common following penetrating injury than following blunt injury. Following penetrating injury, the bowel was most frequently injured; the stomach being injured in 47 per cent, the small bowel in 18 per cent, and the colon in 27 per cent of the 49 patients. Next to the gastrointestinal tract, the diaphragm was most frequently involved, after which came the chest, kidney, liver, and pancreas. Thus, following penetrating injury, the organs most frequently injured were distinctly abdominal; whereas, following blunt trauma, the organs most frequently injured were distinctly extra-abdominal.

Several authors have studied patients with associated renal and splenic injuries. Teasdale[157] recently reviewed this subject, including the few such patients who reached the hospital alive. Neligan,[117] in 1948, found that of 54 patients with renal injuries admitted to a London hospital, only one had a concomitant splenic rupture. Winsburg-White[166] concurred with this finding, noting that only one patient with splenic injury was included in a group of 42 consecutive patients with renal injury who reached the hospital alive. To the contrary, Guterbock,[67] in a post-mortem study, described 36 patients with a ruptured kidney, of whom 13 had associated rupture of the spleen. This high incidence of the associated injuries in the autopsy series clearly indicates the increased magnitude of trauma resulting in the combined injuries. Marion,[110] in 1946, stated that of those patients with a rupture of the left kidney and spleen to reach the hospital alive, the resulting mortality was 50 per cent. In the current series there was only one patient with a fractured left kidney secondary to blunt trauma. This patient survived. Of the 49 patients with penetrating injuries, there were 12 with renal injuries, 5 of whom died (42 per cent mortality).

The increasing magnitude of trauma is clearly reflected in the increasing mortality rate as the mortality is compared with the number of organs injured (Table VIII). Thus, when the spleen alone was injured, the mortality rate was 10 per cent. Thereafter, as the number of injured organs increased, the mortality rate progressively increased, exceeding 60 per cent when five additional organs were injured.

TABLE VIII. ASSOCIATED INJURIES; MORTALITY VS. NUMBER OF ORGANS INJURED (102 PATIENTS; 25 DEATHS)

NUMBER OF ORGANS INJURED	NUMBER OF PATIENTS	NUMBER OF DEATHS	MORTALITY (PER CENT)
Spleen alone	29	3	10
1 additional organ	28	4	14
2 additional organs	22	6	27
3 additional organs	13	5	38
4 additional organs	4	2	50
5 additional organs and over	6	5	83

ANATOMIC TYPES OF INJURY

Table IX correlates the anatomic types of splenic injury with the resulting mortality rate. In this table the single lacerations and the perforations have been grouped into one division. It is not surprising that the group with multiple or stellate fractures and the group with fragmentation of the spleen carry the highest mortality rate (33 per cent). A higher mortality in hilar injuries might have been anticipated but it has been recognized for many years that hilar tears are not necessarily fatal.[7]

An excellent discussion of this subject with appropriate diagrams is contained in Johnson's[85] recent review of 85 patients. Except to note that one of the 11 patients with delayed hemorrhage in the current series had a penetrating instead of a blunt injury, the present study confirms Johnson's observation of a lack of correlation between the anatomic type or degree of splenic injury and the resultant immediate or delayed hemorrhage.

TABLE IX. ANATOMIC INJURY VS. MORTALITY

TYPE OF INJURY	NUMBER OF PATIENTS	NUMBER OF DEATHS	MORTALITY (PER CENT)
Capsular tear only	6	0	0
Single lacerations or perforations (including large tears)	48	14	29
Multiple or stellate tears	12	4	33
Fragmentation of spleen	9	3	33
Tears of splenic pedicle	16	2	12
Multiple or diffuse hemorrhages	7	0	0
Not described	4	2	50
Total	102	25	25

SPONTANEOUS RUPTURE OF NORMAL SPLEEN

The term spontaneous rupture, frequently used in earlier reports,[43, 131, 155, 172] has been used with less frequency in recent years as medical records have become more complete and clinical histories have become more accurate. In almost 100 per cent of patients with delayed rupture or "spontaneous rupture," a history of injury is obtainable postoperatively if not preoperatively. This concept is given added support by the report of delayed rupture described below. Neither the patient nor his family could give a history of trauma preoperatively. Diligent interrogation after surgery disclosed a definite history of trauma. Such a search was not made preoperatively in some of our own patients with delayed rupture. With an increasing awareness of this information by all physicians, a virtual disappearance of the diagnosis "spontaneous rupture of the spleen" can be anticipated. Spontaneous rupture of the diseased or infarcted spleen appears to be an occasional exception to this concept.

CASE 1.—L. B. B., a 32-year-old, white, male alcoholic, was admitted to the Veterans Administration Hospital on Feb. 17, 1955. He was ill, in abdominal distress, and in moderate shock. He had been drinking heavily for fifteen years and excessively for three months. Two weeks prior to admission, he developed constant epigastric pain radiating into his back, anorexia, occasional nausea and vomiting, fever, and chills. A urethral dis-

charge which appeared eleven days prior to admission responded to penicillin. On the day of admission, while attempting to have a bowel movement, the patient suddenly lost consciousness. A history of recent trauma could not be obtained.

Examination revealed an acutely ill, emaciated, pale, slightly jaundiced young man, with a thready and rapid pulse, and blood pressure of 60/30. The abdomen was moderately distended, tender, and rigid. Bowel sounds were hyperactive. The clinical diagnosis on admission was acute pancreatitis.

The patient's hemoglobin was 10.4 Gm. per cent, hematocrit 30 vol. per cent, white blood cell count 32,000. The serum amylase concentration was normal (25 mg. per cent), and the amylase activity of dark bloody fluid aspirated from the abdominal cavity was likewise normal (29 mg. per cent).

He was transfused cautiously and with considerable difficulty because of incompatibilities to all available blood. His condition progressively deteriorated, the anemia increased in spite of multiple transfusions, and he became markedly febrile and disoriented. The abdominal distention increased. Bone marrow studies showed marked hyperactivity of all elements. Liver function studies showed moderate parenchymal dysfunction. It was felt by both the medical and surgical services that the patient's condition was terminal. Because continued conservative therapy would obviously lead to the patient's demise, and because of the lack of an adequate diagnosis, laparotomy was elected. After preparation by transfusion, laparotomy was performed on the third hospital day. The abdominal cavity contained about 2,000 c.c. of old blood which had originated from a large congested spleen (weight 550 grams), with a large stellate laceration. Splenectomy was rapidly performed. The patient's postoperative course was remarkably smooth except for a pelvic abscess which was drained per rectum.

Subsequently his family gave the information, which had nearly been forgotten and which had heretofore been considered trivial, that about one month before admission the patient had been involved in an automobile accident. His car had collided with the rear of another car and the steering wheel had struck him in the left lower chest. The patient and the family were then able to recall that he complained periodically of a nagging left upper quadrant pain and left shoulder pain until increased symptoms began.

RUPTURE OF THE DISEASED SPLEEN

Diseased spleens are more subject to trauma and to rupture than are normal spleens.[8, 56] Many reports of splenic rupture, usually preceded by mild trauma, in patients with spleens diseased by malaria, infectious mononucleosis,[48, 91, 150, 158, 171] chronic and acute leukemia,[56, 64] congestive splenomegaly,[42] sarcoidosis,[82] Gaucher's disease,[111] mycotic aneurysms of the splenic artery,[168] pregnancy,[18, 90] and a number of other conditions reflect the surgical interest in this syndrome. Spleens affected by malaria, infectious mononucleosis, and pregnancy are among the most common in this group.

These acute episodes are often preceded by minimal or, sometimes, no recognized trauma. In three of the patients mentioned above with delayed rupture, in whom a history of minimal trauma was finally elicited, specific mention of old splenic infarction was made by the pathologist while splenic vein thrombosis secondary to chronic pancreatitis was described in two. These spleens were presumably congested or infarcted before their rupture, hence requiring only mild trauma to produce the tear.

Pregnancy.—The first recorded patient with splenic rupture in pregnancy was in 1803.[93] Barnett,[18] in 1952, reviewed this phenomenon and added one patient of his own to the previously reported 27 patients. It occurs more commonly during pregnancy than in labor. Rupture occurred during gestation

in 19 patients: 8, or 42 per cent, of the ruptures occurred in the ninth month, while the other 10 were distributed evenly in the third to eighth month. The associated trauma in the 28 patients was usually mild and occasionally internal, that is, coughing, vomiting, or tenesmus. Seven of the 28 spleens were abnormal for reasons other than pregnancy. Rupture was usually unsuspected because the symptoms and signs were masked by those of pregnancy, although the correct preoperative diagnosis was made in 6 of the 28 patients. Diagnosis late in pregnancy was particularly difficult because of the frequency of concealed accidental hemorrhage of the uterus. Fifteen of the 28 patients died, a mortality of 54 per cent. Barnett concluded that there were no significant changes in the spleen during pregnancy that would predispose it to spontaneous rupture.

DELAYED RUPTURE

As stated, delayed rupture of the spleen has been defined as that rupture which becomes clinically evident 48 or more hours after initial injury. It follows a latent period which is less than one week in 50 per cent and less than two weeks in 75 per cent of patients (27). Table X notes the time of delayed rupture after injury in the current group of 11 patients. Rupture occurred within two weeks in 8 patients (72 per cent). The importance of observing patients with left chest or abdominal injuries for at least two weeks is apparent. The longest interval from trauma to surgery in this series was ten months. Zabrinski and Harkins[170] reported a patient with delayed hemorrhage two years after the initial trauma.

Byrne,[37] in 1952, reported a series of 101 patients with splenic injuries, 27 of whom had the delayed syndrome, in contradistinction to Johnson's[85] report of 35 patients with delayed rupture out of a group of 85 patients.

Blunt injury is nearly always the responsible form of trauma resulting in delayed hemorrhage. One patient in this series was an interesting exception.

CASE 2.—E. H., a 46-year-old colored man, was admitted on Nov. 4, 1953, with a complaint of sudden onset of sharp periumbilical pain radiating into the left side several hours before admission. He was nauseated but did not vomit. There was only minimal left abdominal tenderness. Soon after admission he became febrile. Radiologic studies revealed the presence of a left pleural effusion, displacement of the stomach to the right and anteriorly, depression of the splenic flexure of the colon, and opacification of the left upper quadrant obscuring the splenic shadow. His hemoglobin on admission was 9.2 Gm. per cent; white blood cell count, 12,850. The patient had received multiple ice pick wounds of the left chest and abdomen five weeks earlier. He was explored on Nov. 12, 1953, and a large hematoma about a lacerated spleen was found. Splenectomy was followed by recovery.

TABLE X. TIME OF DELAYED RUPTURE AFTER INJURY (11 PATIENTS)

	1ST WEEK	2ND WEEK	3RD WEEK	4TH WEEK AND LATER
Number of patients	4	4	0	3*
Percentage	36	36	–	27

*30 and 34 days, and 10 months, respectively.

The secondary hemorrhage in patients with delayed rupture is usually precipitated by incidental trauma and is characteristically very sudden in onset. For obvious reasons the diagnosis is more difficult than in patients with immediate rupture, yet no deaths occurred in this group. Such patients usually do not have associated injuries and therefore their total injury is of less magnitude, perhaps accounting for the absence of mortality in our group. The mortality rate in earlier studies was as high as or higher than that for immediate rupture, being 37 per cent in McIndoe's series in 1932.

The explanation for delayed splenic rupture has been discussed by many authors. If the injury is a deep parenchymal wound or a subcapsular hematoma, the lesion may remain small in size without additional trauma, or it may slowly enlarge. This is conceivably the explanation for the persistent or recurrent symptoms in some patients. Additional trauma of minor extent may rupture the capsule over the hematoma producing a sudden severe hemorrhage after the latent period. Should a capsular tear occur as part of the original injury, it has been postulated that a surrounding structure, such as the greater omentum, or a clot occasionally plugs the capsular separation until this mechanism is compromised by secondary hemorrhage.[92]

DIAGNOSIS

Abdominal pain, almost always associated with ruptured spleen, is frequently generalized initially, but by the time a preoperative diagnosis has been made, the pain is, with few exceptions, more pronounced in the left upper quadrant. Other symptoms are inconstant. Left shoulder pain due to diaphragmatic irritation was first described by Kehr[88] and has since been known as Kehr's sign. It was noted by 50 per cent of the patients in this study. Examination reveals, primarily, the signs of peritoneal irritation, secondarily, the signs of acute blood loss. The signs of masked hemorrhage may sometimes be accentuated by having the patient shift rapidly from a supine to a sitting position. Tachycardia, hypotension, nausea, and syncope may result, suggesting the presence of a blood volume deficiency.

In most patients the diagnosis of splenic rupture should be supected if the following criteria are satisfied: (1) history of left-sided injury to chest or abdomen; (2) symptoms and signs of peritoneal and diaphragmatic irritation; (3) the clinical picture of acute blood loss.

Routine hematologic and roentgenologic studies offered little diagnostic assistance. Paracentesis proved valuable when positive. If negative, it probably should be disregarded.

The specific preoperative diagnosis of ruptured spleen was made in only 25 per cent of the patients. It is probably lower in series with a high proportion of associated major injuries. Roettig and associates[135] were able to make the diagnosis preoperatively in only 27 per cent.

Although, in retrospect, the presence of fractured ribs overlying the spleen often made the diagnosis of splenic injury difficult, the time lag prior to surgery in such patients was shorter than in those patients without fractured ribs (Table XI).

TABLE XI. EFFECT OF FRACTURED RIBS ON DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH SPLENIC INJURY (BLUNT TRAUMA)

	PATIENTS WITH RIB FRACTURES (LEFT)	PATIENTS WITH NO RIB FRACTURES
Number of patients	19	18
Average delay from trauma to operation (hours)	9	13
Deaths	2	1
Mortality (per cent)	10	6

MANAGEMENT: MORBIDITY AND MORTALITY

Although the literature of the last fifty years attributes the first successful splenectomy to Riegner, in 1892,[12, 133, 169] Zacarelli, a surgeon of Naples, performed one of the earliest recorded splenectomies in 1549. The patient, a Greek lady, aged 24 years, was the wife of an Italian sea captain. Because of splenomegaly due to quartan fever, the loss of her extraordinary beauty, and the development of a swollen, ulcerated leg, she earnestly requested operation. An incision was made over the spleen, the vessel carefully secured, the entire spleen removed and the wound closed with sutures. The patient recovered. The spleen weighed 1,340 grams. Fioranvanti, a surgeon of Bologna, assisted at the operation. The latter wrote that he had promised the husband to do the operation, but never having done one, he prevailed on the Neapolitan surgeon to undertake it.[55]

Shortly thereafter (1581), a French surgeon at Gian successfully removed a spleen following its injury.[139] This appears to have been the first splenectomy following trauma.

Between 1549 and 1869 there were 26 recorded cases of partial or total splenectomy.[113]

One of the early references to treatment of splenic injury is that of Guthrie[68] in 1855. He advised placing the patient on his injured side, to "seek to avert internal effusion of blood and consecutive inflammation by immobility, cold intra and extra, and immediate compression." By distending the patient's stomach with iced drinks it was thought that contraction of the spleen would be induced.

Conservative treatment of splenic hemorrhage was recognized to carry a prohibitively high mortality by Berger as early as 1902.[23] Between 90-100 per cent of such patients were said to die without treatment.[37, 107, 170]

Splenorrhaphy was first employed by LaMarchia[99] in 1896. He reinforced the suture line with omentum. His mortality rate, using this method, was said to have been 25-50 per cent. Tamponade was practiced at the turn of the last century with some success. Berger[23] reported 10 patients with one death; Quénu[130] reported 15 patients with 2 deaths. Dretzka,[52] in 1930, and Gordon-Taylor,[62] in 1942, stated that suture and tamponade were successful in the treatment of gunshot and other penetrating wounds of the spleen.

Of 3,546 American soldiers with abdominal wounds in World War I, there were only 49 splenic injuries, an incidence of 1.3 per cent.[101] The

operative treatment at that time was tamponade. The mortality among the 49 patients was 63 per cent (Table XII). It is noteworthy that splenectomy was quoted as carrying a 100 per cent mortality.

TABLE XII. MILITARY INJURIES

CONFLICT	NUMBER OF PATIENTS	DEATHS	MORTALITY (PER CENT)
American Civil War	35	33	94.0
World War I[112]	49	31	63.0
World War II			
American[101]	341	85	25.0
British[128]	—	—	15.0*
			25.0†
Korean conflict[141]	79	13	16.5

*Wounds limited to the spleen.
†Splenic wounds with associated injuries.

As direct blood transfusion and transfusion methods were first introduced into this country, some authors[86, 95] advised autotransfusion in the treatment of splenic hemorrhage as a supportive measure. With the advent of blood banks this practice was discontinued.

In World War II[128] there were 341 casualties with splenic injuries operated upon by the Second Auxiliary Surgical Group in 1944-1945. Two hundred ninety-nine of these underwent splenectomy. Of the 42 not so treated, 3 died during operation, drainage, packing and suture was considered adequate in 12, and the remainder were treated inadequately by suture, packing, and, in one instance, by the use of muscle as a hemostatic agent. It was concluded that the efforts expended in trying to avoid a splenectomy were generally wasted, time-consuming, and of more danger to the patient than had splenectomy been summarily performed.

The Korean conflict resulted in an additional reduction in mortality, only 16.5 per cent dying at one forward surgical hospital.[141]

Present-day treatment is to operate as soon as the presumptive diagnosis is made and the initial treatment of shock accomplished. Rapid transfusion and early surgery are sound surgical judgment in the face of active bleeding from a ruptured spleen. It is believed that more lives will be lost due to procrastination than to expedient surgery.

Causes of Death.—Table XIII compares the average time lag from trauma to surgery in patients with blunt and penetrating trauma (immediate hemorrhage). Of the 34 patients operated upon for immediate hemorrhage from blunt trauma, 4 died, a mortality rate of 12 per cent. The time lag between injury and operation averaged ten and one-half hours. Among 48 patients with penetrating injury, there were 12 deaths, a mortality rate of 25 per cent. In the latter group, the average delay was only three and one-half hours. Thus, although patients with penetrating injury were operated upon several hours earlier than those with blunt trauma, the former group had a significantly higher mortality. This higher mortality is understandable because of the

TABLE XIII. MORTALITY OF SPLENECTOMIZED PATIENTS, BLUNT VS. PENETRATING INJURY

	BLUNT	PENETRATING	TOTAL
Number of patients	34*	48*	82
Number of deaths	4	12	16
Mortality (per cent)	12	25	19
Average delay from trauma to operation (hours)	10.5	3.5	6.4
Average number of organs injured	2.0	3.3	—

*Does not include patients with delayed rupture.

greater frequency of multivisceral wounds. Patients with blunt trauma usually require a longer period to establish the diagnosis or the indications for surgery than do those with the more obvious penetrating injury.

In Table XIV the 25 deaths in this series are listed according to their time of occurrence in relation to surgery. Nine patients died before reaching the operating room. These represent 36 per cent of the total mortality. As indicated in Table XV, most of these patients had severe intracranial injuries which were a major primary cause of death. No deaths occurred during surgery. Two-thirds of the deaths occurred postoperatively, chiefly within the first week.

TABLE XIV. TIME OF DEATH IN RELATION TO TREATMENT

TIME OF DEATH	DEATHS	PERCENTAGE OF DEATHS
Preoperative	9	36
Operative	0	—
Postoperative	16	64
Day of operation	5	20
1st or 2nd day	3	12
3rd-7th day	5	20
After 1st week	3	12
Total	25	100

Although the identification of a single cause of death is not entirely accurate, it often permits a better appreciation of the major problems. Table XVI indicates that 48 per cent of the fatalities were due directly to hemorrhage. Inclusion of the three patients who died of post-traumatic renal insufficiency would increase to 60 per cent the incidence of hemorrhage as the direct or indirect cause of death. Two-thirds of these were due primarily to hemorrhage from an associated injury. One patient died because of a fulminating intraperitoneal infection, 7 patients (28 per cent) from associated intracranial injuries, and 2 patients (8 per cent) suffered catastrophic cardiac or pulmonary complications postoperatively.

The importance of hemorrhage as a cause of death and the prognostic significance of shock at the time of admission is further substantiated by Table XVII. As shock increased in severity, the mortality rate increased sharply. This fact was borne out not only by a correlation of mortality rates with the admission blood pressure, but also with the subsequent transfusion requirements (Table XVIII) and finally with the autopsy findings (Table XVI).

TABLE XV. CAUSE AND TIME OF PREOPERATIVE DEATHS*

PATIENT AND YEAR	INTERVAL FROM ADMISSION TO DEATH	DIAGNOSIS	CAUSE OF DEATH
1945	Few minutes after admission	Ruptured spleen	Hemorrhage from spleen
1946	5 days	Fracture of pelvis; chest injury; ruptured spleen (unrecognized)	Coronary occlusion
1947	Few minutes after admission	Head injury; chest injury; ruptured spleen	Head injury
1947	11 hours	Ruptured right auricle; ruptured spleen	Ruptured right auricle
1948	12 hours	Head injury; ruptured spleen; chest injury	Head injury
1948	12 hours	Head injury; ruptured spleen	Head injury
1950	1 hour	Head injury; chest injury; ruptured spleen	Head injury
1951	Few minutes after admission	Head injury; fracture of femurs; lacterated spleen and liver	Head injury
1952	2 hours	Head injury; chest injury; ruptured spleen	Head injury

*Each patient admitted approximately one hour after injury.

TABLE XVI. CAUSES OF DEATH (25 PATIENTS)

CAUSE	PRIMARY CAUSE OF DEATH	PERCENTAGE OF DEATHS	MAJOR CONTRIBUTING CAUSES OF DEATH
Hemorrhage	12	48	—
From associated injury	8	—	6
From spleen	4	—	—
Infection	1	4	—
Post traumatic renal failure	3	12	—
Primary intracranial injury	7	28	2
Cardiac infarction or pulmonary embolism	2	8	—
Thoracic injury	—	—	2
Wound dehiscence	—	—	1
Postoperative intestinal obstruction	—	—	2

TABLE XVII. MORTALITY RATE VS. ADMISSION BLOOD PRESSURE (SYSTOLIC)

BLOOD PRESSURE	NUMBER OF PATIENTS	NUMBER OF DEATHS	MORTALITY (PER CENT)
Over 100 mm.	35	3	8
50-100 mm.	52	14	27
0-50 mm.	15	8	53

TABLE XVIII. MORTALITY RATE VS. TRANSFUSION REQUIREMENTS (DAY OF ADMISSION)

TRANSFUSION REQUIREMENTS	NUMBER OF PATIENTS	NUMBER OF DEATHS	MORTALITY (PER CENT)
0-500 ml.	29	5	17
501-1,000 ml.	40	9	22
Over 1,000 ml.	33	11	33

Comparative mortality rates between the periods 1945-1947 and 1948-1955 are shown in Table XIX. This distinction is based on the fact that blood bank facilities were first fully developed in the hospitals in 1948. In addition, it was then that the residency program at this institution was implemented to such an extent that medical care of emergencies was improved. A decrease in mortality from 33 per cent during the first period (1945-1947) to 23 per cent for the last period (1948-1955) resulted. However, when those patients who died within one hour of admission to the hospital were excluded, the mortality rate barely changed.

TABLE XIX. MORTALITY RATE FOLLOWING SPLENIC INJURY

PERIOD OF STUDY	ALL PATIENTS			EXCLUDING PATIENTS DYING WITHIN ONE HOUR AFTER ADMISSION	
	NUMBER OF PATIENTS	NUMBER OF DEATHS	MORTALITY RATE (PER CENT)	NUMBER OF PATIENTS	MORTALITY RATE (PER CENT)
1945-47*	15	5	33	13	23
1948-55†	87	20	23	85	21
Total	102	25	24	98	21

*Penicillin available.
†Adequate blood bank facilities.

The experiences in this study have reflected the improving care in other institutions. In Table XX, which summarizes the mortality rates in other civilian institutions during the past half century, a progressively decreasing mortality rate is evident.

TABLE XX. MORTALITY RATES IN CIVILIAN EXPERIENCES

DATE	AUTHOR	NUMBER OF PATIENTS	MORTALITY RATE (PER CENT)
1900	Bessel-Hagen[24]	37*	46
1908	Lotsch[77]	138*	38
1928	Conners[44]	25	40
1932	McIndoe[107]	46	37
		37*	27
1939	Wright and Prigot[169]	30	43
		22*	23
1941	Rousselot and Illyne[138]	17*	29
1943	Roettig[135]	22	32
		15*	7
1950	Byrne[37]	101	17
1954	Johnson[85]	85	20
1955	Present series	102	24
		93*	17

*Asterisks indicate operative mortalities, while the figures in the remainder of the series listed represent mortality for entire groups including those who died without or before surgery.

Nonfatal Complications.—Twenty-four major nonfatal complications occurred among the 77 surviving patients (Table XXI). Thoracic complications were most common; wound complications were next in frequency, there being two wound abscesses and two wound dehiscences. These experiences roughly parallel those of previous reports. Neither splenosis nor splenic vein thrombosis was encountered. Among the surviving patients, the average hospital stay for

those patients without complications was eight and one-half days, for those with complications twenty days; the over-all average for the survivors being thirteen days.

TABLE XXI. POSTOPERATIVE COMPLICATIONS (NONFATAL)

COMPLICATION	NUMBER OF PATIENTS	PERCENTAGE OF COMPLICATIONS
Chest	6	25
Severe atelectasis	1	
Hemopneumothorax	5	
Wound	4	17
Abscess	2	
Dehiscence	2	
Central nervous system	2	8
Cerebrovascular accident	1	
Psychosis	1	
Peritonitis or intra-abdominal abscess	4	17
Intestinal obstruction	1	4
Urinary tract infections	2	8
Intestinal fistula	1	4
Pancreatitis	1	4
Unexplained fever (marked)	2	8
Phlebitis	1	4
Total	24	100

EFFECTS OF SPLENECTOMY

The effects of splenectomy upon the patient have received little attention from most authors. Those who have followed splenectomized patients (for rupture of the normal spleen) have found a few fairly consistent alterations:[76, 106, 125, 167] (1) a persistent anemia, which usually returns toward normal within several months; (2) a decrease in the number of platelets which is usually temporary; (3) a moderate enlargement of many of the superficial lymph glands; (4) the red blood cells demonstrate an increased resistance to destruction; (5) the output of iron in the stools is increased; (6) there is an increase in total blood cholesterol.

SPLENOSIS

Splenosis was the term given by Buchbinder and Lipkoff,[31] in 1939, to the phenomenon recognized years before as the occurrence of multiple peritoneal splenic implants following traumatic rupture of the spleen. Only 26 cases had been described as recently as 1953.[74] An illustrative case follows.[103]

CASE 3.—A 29-year-old white man was admitted with a complaint of severe abdominal pain, vomiting, and constipation. At the age of 14 a crushing abdominal injury necessitated the removal of a ruptured spleen.

On the latter admission, laparotomy revealed that the bowel was moderately distended and studded with small, sessile, greenish black tumors. The visceral peritoneum likewise was covered with these nodules which varied in diameter from pin-point to one inch. There was an estimated 200 to 300 of these splenic implants. The band causing the obstruction was divided and the abdomen closed.

The rarity of splenosis is probably due in part to the fact that rupture of such degree as to fragment a spleen is often associated with immediate death. The true incidence is doubtlessly unknown because of the small number of autopsies performed on splenectomized patients.[154]

The first accepted reference to this complication was by Griffini and associates,[65] in 1883, when he observed spleenlike nodules in the peritoneum of dogs following partial splenectomy. The first patient reported by Von Kuttner[159] was regarded at that time as having congenital accessory spleens although they were not found until four years after rupture of the spleen. Faltin,[54] in 1911, first suggested that such nodules might represent splenic implants.

The pathogenesis of this phenomenon has not been completely settled. Splenosis has not been observed following removal of diseased spleens except for one authenticated patient with thrombocytopenic purpura.[153] Instead, it appears to follow injury or removal of the normal spleen. This is especially evident in Egypt where many splenectomies are performed due to bilharziasis and other infections.[148]

Several theories of the pathogenesis have been examined by Hartmann[74] in his recent review. The following was found to be the most tenable:

> The transplantation or "seeding" theory. This is similar to Samson's[142] theory of endometriosis and is the most logical explanation for splenosis. Splenic implants as contrasted to accessory spleens (vida infra) have been found in such distant locations as to be incompatible with an embryological origin.

Mention has been made in the literature that splenosis resembles the normal condition found in some invertebrates and higher fish, in which the spleen is absent and small bits of splenic tissue are found scattered in various parts of the abdomen.[162] The first experimentally produced autograft was produced in the rabbit by Manley and Marine[109] in 1917. Since then similar experiments have been reproducible in other animals such as mice and rats.[38] These experiments would suggest the theory described above.

Clinically, there is always a history of trauma, a ruptured spleen, and splenectomy in a young individual. The average age of the 26 reported patients is 10 years; there were only 3 over the age of 30 years. The shortest interval from trauma and surgery to the discovery of splenosis in the human is six months.[98] The implants are most frequently found in the visceral peritoneum, as many as several hundred having been found in a single patient. In one patient 82 implants were found distributed over the peritoneal cavity, the diaphragm, the greater omentum, the pouch of Douglas, the left pleural cavity, the eighth dorsal vertebra, and beneath the capsule of the left lobe of the liver. Other recorded sites include the abdominal wound, the body wall,[59] the scrotum, and the parietal peritoneum.

Symptoms produced by splenic implants are usually vague abdominal pains and, eventually, those of obstruction as multiple adhesions form between implants and adjacent loops of bowel. The diagnosis is rarely if ever made preoperatively. It is impractical or impossible to remove the plants. Surgical treatment in most instances consists of lysis of adhesions.

Splenosis must be differentiated from accessory spleens. The latter are very common; the incidence in autopsy series being about 10-20 per cent in younger age groups.[1, 45] Other differential generalities are: (1) accessory spleens are fewer in number, usually 2 to 6; (2) eighty-five per cent of accessory spleens occur in one location; (3) the majority of accessory spleens occur at or near the hilum of the spleen. Ninety-eight per cent of them occur in the region of the spleen; (4) accessory spleens are miniature adult spleens, with identical structure. Autoplastic spleens have no hilum or true capsule. The only tissue of splenic origin is the pulp. The capule is derived from surrounding connective tissue and it forms irregular trabecules. The blood supply is derived from the periphery. The follicles are somewhat irregular.

While splenosis is admittedly a rare phenomenon, it is of importance in dealing with rupture of the normal spleen in a young individual. In performing a splenectomy in such circumstances it might seem desirable for the surgeon to:[74] (1) eliminate spillage of splenic pulp or rupture of the capsule; (2) carefully clear the abdomen before closure; (3) protect the incision from contamination with splenic pulp to avoid seeding the subcutaneous tissues; (4) eliminate autotransfusion unless no other blood is available. There is a theoretical possibility of disseminated splenosis. However, there are no reported cases of nodules in either lung although several patients with ruptured spleens have received filtered intraperitoneal autotransfusions of whole blood.

Such suggestions are not based on the assumption that regeneration is harmful per se, but that the incidence of secondary complications appears high.

SUMMARY

Of 102 patients with ruptured spleens treated over the ten-year period from 1946 to 1955, 49 had received penetrating injuries and 53 blunt injuries. Associated injuries to other organs were present in 72 per cent of the total series. Thoracic injuries, fractures, and intracranial injuries were often associated with the splenic injury caused by blunt trauma. With penetrating wounds, injury to the intestinal tract was the most frequent complicating injury. Following the two types of injury, the mortality of patients reaching the hospital alive was the same, 24 per cent. Approximately one-third of the patients died preoperatively, chiefly of intracranial injuries secondary to blunt trauma. Of the total deaths in the entire period (25 patients), 48 per cent were due directly to hemorrhage, 28 per cent to intracranial injury, and 12 per cent to post-traumatic renal insufficiency. Mortality rates were directly proportional to the magnitude of injury as represented by the total number of organs injured. When the spleen alone was injured, the mortality rate was only 10 per cent.

Of the patients with penetrating injuries, bullet wounds were the most common mode of injury and resulted in the highest mortality rate (44 per cent). There were no deaths among the 21 patients with stab wounds. Of

the 53 patients with blunt injuries, auto accidents comprised the largest group (34 patients) and resulted in a 26 per cent mortality rate. Falls resulted in the injury of 8 patients, three of whom died (37 per cent).

Of the 91 patients who had immediate rupture, 25 died, a mortality rate of 27 per cent. Eleven patients had a delayed rupture, none of whom died.

Following splenectomy for immediate rupture, the mortality from penetrating injuries (25 per cent) was higher than that from blunt trauma (12 per cent), although there was a significantly shorter time lag prior to surgery in the former group. The higher mortality was due to the high incidence of associated injuries in the patients with penetrating injuries who underwent operation.

The correlation between the anatomic type of splenic injury and the mortality rate is not remarkable in this series. Multiple and stellate fractures as well as fragmentation of the spleen resulted in the higher mortality rates. Hilar injuries were associated with only a 12 per cent mortality rate.

Three-fourths of the patients with delayed hemorrhage bled secondarily within two weeks of the initial injury, a fact which suggests that patients suspected of having a splenic contusion should be warned of this possible complication.

Improvements in therapy during this ten-year period have resulted from improved blood bank facilities and improvements in emergency care by the resident surgeons. Additional progress depends primarily upon the improvement of techniques in controlling intra-abdominal hemorrhage.

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Calendar of Surgical Meetings

1956

THE AMERICAN ACADEMY OF NEUROLOGICAL SURGERY. *Annual Meeting,* Nov. 1-3, 1956, Camel Back Inn, Phoenix, Ariz. Secretary, Eben Alexander, Jr., M.D., Bowman Gray School of Medicine, Winston-Salem, N. C.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA. *Annual Meeting,* Oct. 4-6, 1956, The Biltmore, Santa Barbara, Calif. Secretary, James K. Stack, M.D., 700 N. Michigan Ave., Chicago 11, Ill.

AMERICAN COLLEGE OF SURGEONS. *Clinical Congress,* Oct. 8-12, Civic Auditorium, San Francisco, Calif. Secretary of the College, Michael L. Mason, M.D., 154 E. Erie St., Chicago 11, Ill.

AMERICAN MEDICAL ASSOCIATION. *Clinical Session,* Nov. 27-30, 1956, Civic Auditorium, Seattle, Wash. Secretary, Council on Scientific Assembly, A. M. A., 535 N. Dearborn St., Chicago 10, Ill.

LATIN AMERICAN CHAPTER OF INTERNATIONAL SOCIETY OF ANGIOLOGY. *Third Meeting,* Nov. 8-11, 1956, Havana, Cuba. President, Armando Núñez Núñez, Calle 25 No. 510, Vedado, Havana, Cuba.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 5 and 6, 1956, Poland Springs House, Poland Springs, Maine. Secretary, Richard Warren, M.D., Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 4-6, 1956, the Boca Raton Club and Hotel, Boca Raton, Fla. Deadline for papers, Sept. 20, 1956. Secretary, George G. Finney, M.D., 2947 St. Paul St., Baltimore, Md.

1957

AMERICAN UROLOGICAL ASSOCIATION. *Annual Meeting,* May 6-9, 1957, William Penn Hotel, Pittsburgh, Pa. Deadline for papers, Jan. 1, 1957. Secretary, Samuel L. Raines, M.D., 188 S. Bellevue Blvd., Memphis, Tenn.

THE CENTRAL SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 21-23, 1957, The Drake Hotel, Chicago, Ill. Deadline for papers, Oct. 15, 1956. Secretary, Charles D. Branch, M.D., 102 North St., Peoria, Ill.

THE PACIFIC COAST SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 4-6, 1957, El Mirador Hotel, Palm Springs, Calif. Secretary, Carleton Mathewson, Jr., M.D., Stanford University Hospital, San Francisco 15, Calif.

PAN-PACIFIC SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 14-22, 1957, Honolulu, Hawaii. Director General, F. J. Pinkerton, M.D., Room 230, Young Building, Honolulu, Hawaii.

THE SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 7-9, 1957, Columbus, Ohio. Secretary, James Hardy, M.D., Hospital of the University of Mississippi, Jackson, Miss.

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